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1. STUDY THE EFFECT OF WET GRANULATION AND FUSION METHODS ON PREPARATION, CHARACTERIZATION, AND RELEASE OF LORNOXICAM SACCHAT EFFERVESCENT GRANULES

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Effervescent granules are formulated to reduce slow absorption which are intended to be dissolved or dispersed in water before use. This dosage form includes a mixture which when incorporated in water, produces an immediate rate of release of the therapeutic compound for instant release [1].

The present work is based on the formulation of effervescent granules of Lornoxicam unit dose. Six such formulations were prepared using citric, tartaric acids and sodium bicarbonate as effervescent base at different ratios. Mannitol and aspartame were used as sweetening agents since lornoxicam has bitter taste. The granules were produced by the wet and fusion method, they were evaluated for flow property (like angle of repose, bulk density, tapped density and Carr's index), particle size, pH, effervescence time, in vitro dissolution studies and drug content. The formulated effervescent granules exhibited excellent flow properties and bulk density suitable for a unit dose. All the formulations exhibited effervescence time less than 60 sec and dissolution profile was found to be more than 75% in 5 mins. F2 formulation was selected as the best formulation because of their physicochemical characteristics; it is concluded that wet method resulted in better granules compared to fusion method.

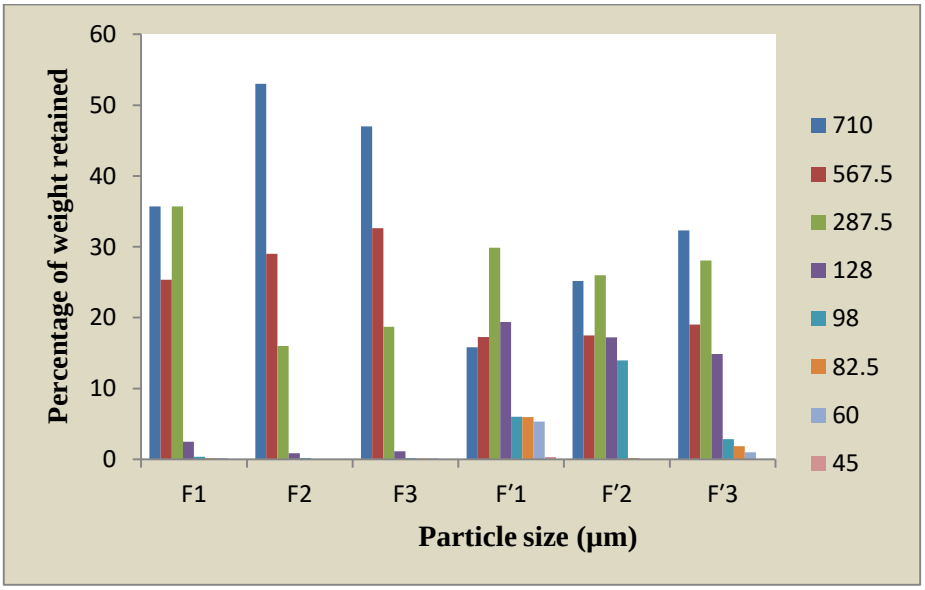

Figure 1. Particle size distribution

[1] Bhattacharyya S, Swetha G. Formulation and evaluation of effervescent granules of Fexofenadine hydrochloride. The Pharma Innovation. 3 (2014)1-8.

2. ECONOMY OF GRANULATION VS INDUSTRIAL PRODUCTION CHALLENGES

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Before the first technical drying processes were developed by the industrial revolution of the XIXth century, natural drying processes such as drying in the sun, direct firing, filtration or similar, often natural processes were used to remove water from the products. This allowed the products to be preserved and used for further processing. The division of the 'dewatering processes' into thermal and mechanical was made for the first time at the beginning of the XXth century and has been broken down in increasing detail to this day. As a result, a large number of different technologies can now be assigned to processes that have adapted to the increasing requirements of products and the sales market.

Today's markets require a high degree of flexibility with regard to the adaptability of plant technology. Each product has specific requirements that must be met. The challenge is to achieve a balance between rising production costs and the required profitability through cost-efficient production without losing sight of the increased product requirements. In addition, product development time has been significantly reduced due to the fast-moving markets, so that another critical factor has to be taken into account.

One solution is to outsource production to a contract service provider specializing in the production of high-quality; customer-specific granulates and powders. Due to the wide range of possible applications of fluidized bed spray granulation systems, it is possible to achieve synergy effects and at the same time to meet the individual requirements of customers. In addition, the time from development to market readiness of a product is shortened so that trends can be responded to more quickly. Also, the costs for misinvestments due to products not accepted on the market can be avoided and new investments can be postponed to a later date.

In the course of the presentation it will be shown that the economy of scale effects such as the combination of stand-alone campaigns into combined campaigns, the use of synergy effects, the short-term use of large-scale plants, shorter transport routes within production, focusing on high volume products in combination with specialisation in fluidised bed technology can increase profitability despite increased market and product requirements.

3. A DEM STUDY OF RELATIONSHIP BETWEEN MECHANICAL STRENGTH AND GEOMETRICAL PARAMETERS OF AGGLOMERATES COMPOSED OF PLANT MATERIALS

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Among few components of agglomerates, plant materials (e.g. fodders, sawdust, starch, cellulose microcrystalline) constitute a significant group. The granular plant materials are nonuniform in size and characterized by a certain degree of polydispersity what strongly affects mechanical strength of agglomerates (shear strength, compression strength and tensile strength). Many experimental and theoretical studies based on continuum mechanics have been carried out to study the macroscopic mechanical responses of compacts, however, the lack of physical interpretation of numerous experimental effects observed in grain beddings results in development of numerical techniques which allow for detailed analysis of granular materials. Among these techniques, a discrete element method (DEM) is one of currently available technique that can provide insight to the problem of powder compaction at the particle level [1]. Over last few decades, the extensive studies on the agglomeration of agriculture materials have been conducted aimed to analyse the load-deformation behaviour of compacts [2,3], however, a few issues relating these products remain still unsolved.

Because of the strong relationship between the mechanical strength of agglomerates and the geometrical parameters of particles, the analysis of the impact of shape and particle size heterogeneity on the interactions between particles in compressed agglomerates composed of granular plant material was conducted. Numerical simulations of mechanical tests, including compression tests and tensile tests were conducted by using EDEM package [4]. Simulations were conducted with non-linear elastic-plastic model with adhesion. Tablets composed of 120 thousands of particles with material parameters of potato starch were compressed up to 150 MPa. The numerical results were compared with experimental data obtained for 0.5 g samples of potato starch with moisture content of 12 and 17%.

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[2] P.L Bellinger, H.F. McColly, Energy requirements for forming hay pellets. Agric. Eng., 42, (1961), 244-247.

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[4] EDEM Software (2016). www.dem-solutions.com/software/edem-software

4. EXPERIMENTAL STUDY ON THE ELECTROSTATIC CHARACTERISTICS OF L-ISOLEUCINE POWDER

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Amino acids are important in nutrition and are commonly used in nutritional supplements, fertilizers, and food technology because of their biological significance. Because amino acid powders are usually treated in clean rooms with low humidity out of the necessity for quality management, electrostatic charge build-up is apt to occur easily. Thus, risk assessments for amino acid powders are necessary to prevent electrostatic accidents. As powder sample, L-isoleucine, an amino acid powder, is used in this experiment. In this experiment, a conventional volume resistivity test cell, the spiral air tribocharge apparatus, and the commercial MIE test apparatus [1] employed for measuring the resistivity, the charge-to-mass ratio, and the ignitability of L-isoleucine powder, respectively.

From the test results, we concluded that L-isoleucine powder has a volume resistivity as high as 1.2 × 1013 Ωm or higher, classified as highly electrifying, with a high risk of electrostatic charge. The actual charge-to-mass ratio was 6.4 nC/g on average. Additionally, with an MIE of 4 mJ, this material is very sensitive to electrostatic discharge (refer Fig. 1). Therefore, the present findings suggest that industrial processes using L-isoleucine powder must be carefully managed, since it is always possible that industrial accidents due to electrostatic charges and/or discharges can occur.

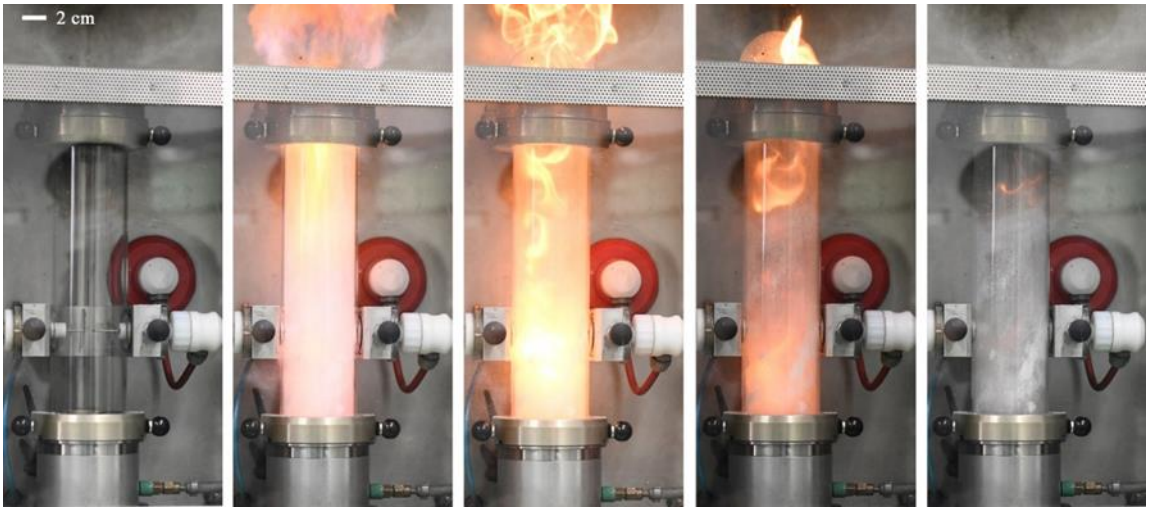

Figure 1. Typical sequence of L-isoleucine dust explosion observed with a commercial MIE test apparatus.

[1] IEC, International standard 61241-2-3, 1994.

5. EFFECT OF AGITATING CONDITIONS OF INTENSIVE MIXER ON AGGLOMERATION OF IRON ORE

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In ironmaking process in steel mills, powdery iron ores as raw materials are made to sintered ore for the permeability of a blast furnace. As major process for making sintered ore, Dwight-Lloyd-type is appllied to a lot of steel mills. In this process, iron ores and bonding agents (carbon-based fuel etc.) and others are mixed and sintered by carbon combustion with air. Therefore it is important to agglomerate them for permeability in the sintering machine. On the other hand, in the point of recent conditon of environment, high-grade iron ore, which have high Fe contents, is required to be used in the steel mills because Fe% of standard iron ores rapidly decreases. Since high-grade iron ore is very fine compared with standard iron, it is difficult to agglomerate them by the conventional mixer such as drum mixer [1].

In previous works, it was reported that the agitating high-grade iron ore by intensive mixer was effective on the agglomeration as pre-treatment before a conventional mixing process[2]. Moisture contents in the iron ore become homogenious by the agitation with large shearing force of intensive mixer and therefore size distribution of agglomerates after conventional mixer could be narrow and the peameability in the sintering maching could be improved. However size distribution change after intensive mixing on each condition has not been investigated well so far compared to drum mixer and pelletizer.

In order to utilize much amount of high-grade ores, it is necessary to control the agglomerate's structure based on the understanding of granulation and collapse and agglomerate phenomenon in intensive mixer. In this work, the effect of the mixing conditon on intensive mixer on the moisture and particle size distribution was investigated. From these results, the behavior of the mosture and iron ore on the agglomerates in intensive mixer was discussed.

[1] O. Komatsu, H. Noda, H. Fukuyo and N. Sakamoto, Evaluation of granulation characteristics and properties of quasi-particles using a large amount of iron ore fines, CAMP-ISIJ, 5 (1992) 1042.

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6. SHAPING OF COMPLEX ALUMINA COMPONENTS VIA LASER ADDITIVE MANUFACTURING OF SPRAY-DRIED CERAMIC GRANULES

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2 Institute of Ceramic, Glass and Construction Materials, TU Bergakademie Freiberg, Agricolastraße 17, Freiberg, Germany
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Shaping of complex geometries with high precision and having both high strength and fracture toughness of the workpiece material is a key challenge in ceramics processing. This is in combination with long processing time and cost-intensive post processing a major obstacle for a broader application of high tech ceramic parts. Selective direct laser sintering and melting (SLS/SLM) could be a solution to these problems. Being an emerging technology in metals and polymer processing, severe problems like crack formation and weak densification have to be still approached for the production of high performance ceramics.

The absence of understanding the interaction of laser light sources with the ceramics based materials and the slow sintering kinetics of ceramics is today the cause of no existing SLS process available to consolidate ceramic powders to dense structures with convenient material properties in high tech ceramics.

Based on our approach the starting ceramic nanosized powders are granulated by spray drying to achieve a high flowability, a high powder bed packing density for solid and liquid phase sintering and a fast and failure free densification. The variation of the composition and morphology of these doped nanocomposite granules affects the absorption behavior to the applied laser light. The focus here is on the optimization of particle size, raw powders ratio and additives to improve the interaction between the laser and the granules. The reduction of thermal stresses and cracks formation during laser-processing is also a major challenge to be solved in the ongoing work.

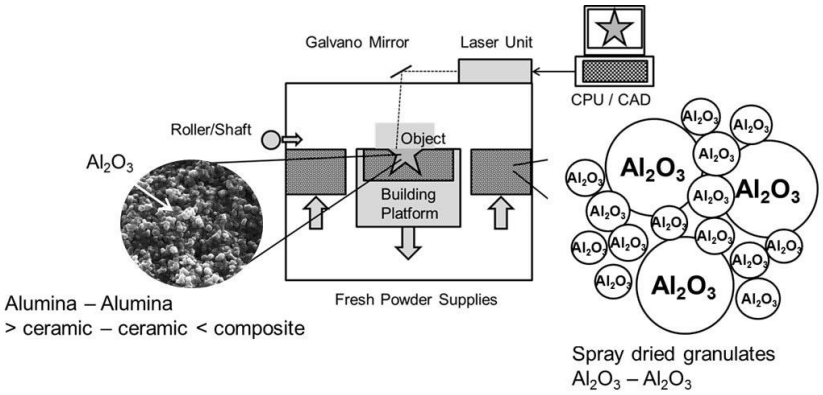

Figure 1. Process of SLS/SLM of spray-dried ceramic granules

7. MONTE CARLO MODELLING OF SPRAY FLUIDIZED BED AGGLOMERATION

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Spray fluidized bed agglomeration is a size enlargement process consisting of many micro-mechanisms like binder addition, collision, adhesion, bridge formation, drying and breakage mechanism. Monte-Carlo method is a stochastic tool to simulate complex particulate processes (such as spray fluidized bed agglomeration) by taking into account various (or all) micro mechanisms that can possibly affect the overall (macro) behavior of the system. Event driven constant volume Monte Carlo (CVMC) method is used in the present work, where an "event" is defined as one collision between the particles within the fluidized bed and the time step is calculated according to the time associated with this collision.

The morphological descriptors of the agglomerates formed are vital in understanding the properties of the final product. The model from [1] can easily predict the kinetics of the process under the variation of several process parameters. However, the morphology of the final agglomerates is not captured, because the agglomerates were assumed to be spherical particles of constant porosity, with quite an arbitrarily chosen value of 0.6. In the present work, a cross-correlation between the various morphological descriptors is formulated and validated with various literature and experimental results [2]. Subsequently, a new CVMC model is generated using this correlation to predict the morphology of the agglomerates formed as well as the kinetics of the process at different operating conditions.

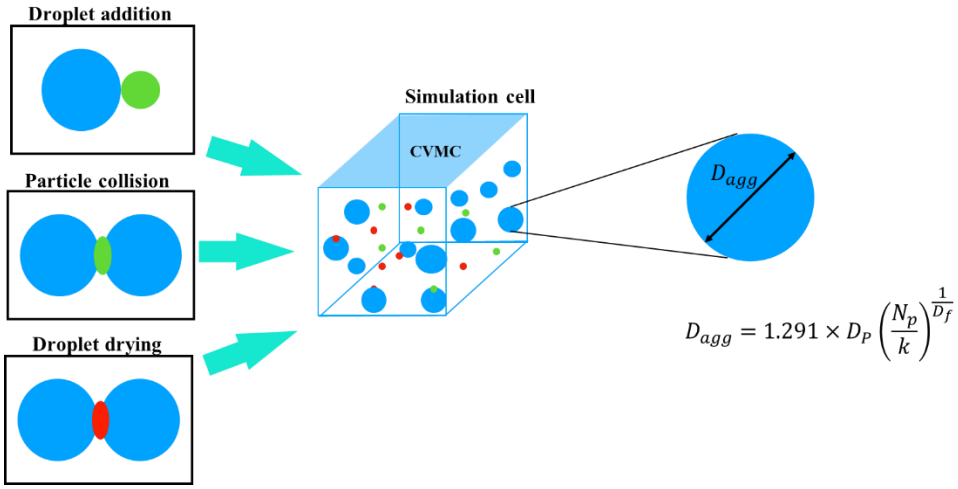

Figure 1. Schematic representation of CVMC

[1] K. Terrazas-Velarde, M. Peglow, E. Tsotsas, Stochastic simulation of agglomerate formation in fluidized bed spray drying: A micro-scale approach, Chem. Eng. Sci., 64 (2009) 2631–2643.

[2] M. Dadkhah, E. Tsotsas, Influence of process variables on internal particle structure in spray fluidized bed agglomeration, Powder Technology, 258 (2014) 165–173.

8. MODELING OF UNDESIRED AGGLOMERATION IN FLUIDIZED BED COATING

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Fluidized beds are widely used in the pharmaceutical, agricultural, and food industry to produce particulate products from liquids containing solid material. The liquid is sprayed on a fluidized bed of particles inducing size enlargement either by agglomeration or layering. Agglomeration denotes the formation of larger particles consisting of several initial or primary particles, which are in this case connected by material bridges. In layering the particles grow by repeated droplet deposition, drying, and solidification of the liquid droplets. As a result, a solid layer is formed around the initial particles. In principle both mechanisms occur simultaneously, but depending on the purpose of the process, only one of them should be dominant. The question is how the process conditions and material properties need to be chosen to promote the desired size enlargement mechanism.

This study deals with undesired agglomeration during a fluidized bed coating process. A process model is presented consisting of heat and mass balances as well as a population balance model for layering growth. Partial wetting of particles is taken into account by introducing the degree of wetting based on the droplet geometry. The well-known Stokes criterion [1], which is often used to estimate if a binary collision is successful and leads to agglomeration, is incorporated into the model. This enables the calculation of a critical diameter: particles having a diameter above the critical value grow by layering while smaller particles may agglomerate. The influence of process parameters (temperature, spraying rate, mass fraction of the solid material in the liquid) and droplet properties (droplet size, contact angle) on the fraction of particles below the critical diameter (agglomeration fraction) is investigated in a simulation study.

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9. ALL YOU NEED IS TWO TABLETS - HOW AXIAL RECOVERY IS THE KEY TO A PRECISE OUT-OF-DIE TABLET DENSITY PREDICTION

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Tablet density as a function of compaction pressure is valuable information during the development of a tablet formulation. However, getting a full out-of-die density profile is labour intensive and requires at least a few grams of material. During early development, material sparing methods are advantageous since even a few grams of active ingredients might not be available. This work introduces an easy to adopt method to predict an accurate full out-of-die density profile based on two tablets.

Two key observations that enable the prediction are: 1) in- die axial elastic recovery increases linearly with increasing compaction pressure and 2) the axial elastic recovery after ejection of a tablet is independent of compaction pressure (Figure 1A). Two tablets compacted at low and high pressures, respectively, are needed to establish the linear relationship and to identify the out of die elastic recovery. The two observations were confirmed using compaction data of 47 model powders collected in two laboratories using two different compaction simulators by four operators. These powders exhibit a wide range of compositions (common tablet excipients, binary mixtures, placebo formulations, and active tablet formulations) and mechanical properties (plastic, viscoelastic, and brittle). Based on these and by taking into consideration of the radial recovery, a full out-of-die density profile could be predicted. The predicted density profile is further corrected using the measured density of the two tablets to attain nearly perfect match between the predicted and experimental tablet density - pressure profiles (Figure 1B). The good accuracy of the predicted density profile makes it possible to predict the true density of a material and obtain a plasticity parameter by model fitting [1].

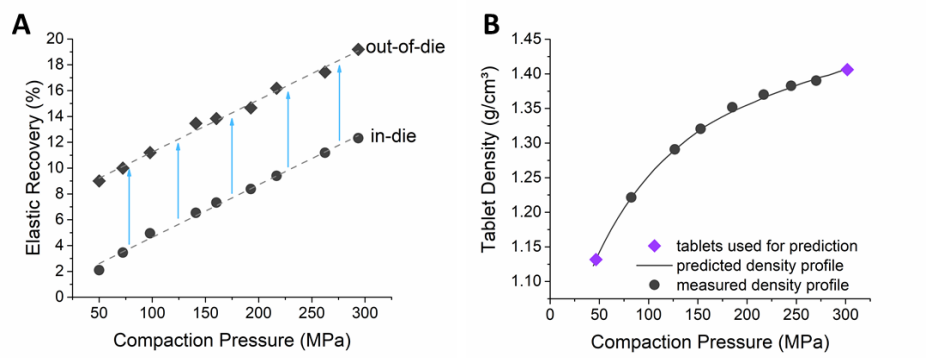

Figure 1. Example of lactose monohydrate A. axial elastic recovery in-die and out-of-die showing the compaction pressure independence of out-of-die elastic recovery. B. predicted versus measured density profile

[1] Sun CC. A novel method for deriving true density of pharmaceutical solids including hydrates and water-containing powders. J Pharm Sci. 93 (2004) 646–53.

10. INVESTIGATION OF CONTINUOUS WURSTER GRANULATION WITH EXTERNAL PRODUCT CLASSIFICATION

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Wurster granulation can be used for coating and layering applications for powders and larger bulk materials. Although the batch-wise Wurster granulation is widely applied, its continuous operation with external product classification provides the advantage of higher productivity. However, the continuous mode requires a process control strategy to achieve process stability, which has already been stated as stabile in former researches of Hampel [1]. The present contribution investigates Hampel's strategy, which includes a feed-back controller of the fluidized bed mass manipulating the classifier gas velocity. However in contrast to Hampel's work, a targeted formulation of the desired product specification is supplemented to the process control strategy. Therefor a simplified particle growth model has been developed which predefines the required spray-to-feed ratio as well as a set classifier gas velocity of the controller to achieve a desired product mean diameter. Further the separator particle inlet mass flow rate is introduced as a new model constant which has been fitted experimentally. These innovations are implemented into the two-zone population balance model used in Hampel [1] and the simulation results for different desired particle sizes and various process conditions are shown here.

The experimental part of this contribution includes batch experiments (Fig. a) in the first instance, from which spray rate losses and effective coating layer densities are determined to confirm the required spray-to-feed ratio of the continuous granulation experiments. In the second instance, the fluidized bed mass and product properties of continuous experiments for various parameter settings are shown (e.g.: dry spray rate, see Fig. b) and compared with simulation results to discuss the here suggested process control strategy.

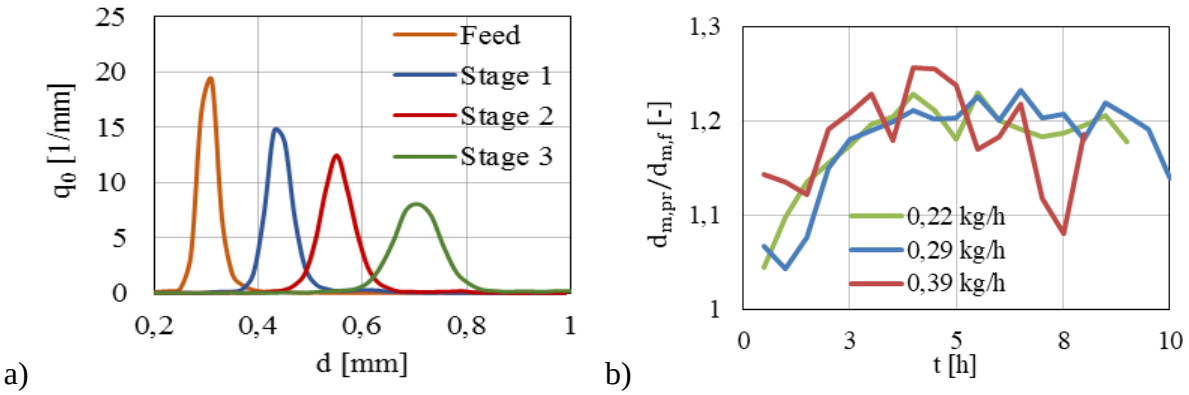

Figure 1. a) PDS of multi-stage batch experiments. b) Relative product size of continuous experiments.

[1] N. Hampel, A. Bück, M. Peglow, E. Tsotsas, Continuous Pellet Coating in a Wurster Fluidized Bed Process, Chemical Engineering Science, 86 (2003) 87 – 98.

11. THE EFFECT OF TARGET-PARTICLE SHAPE ON THE BREAKAGE AND ADHESION OF AN IMPACTING AGGLOMERATE

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Understanding the collision between an agglomerate of fine particles and a target is the primary step to gain a deeper knowledge on the adhesive mixing process. While the effect of several variables such as collision velocity, particle interface energy, and size distribution on the collision behaviour have been largely explored, the effects of target morphology have yet to be revealed. In this work, 3D target particles with controllable shape and texture have been generated using Fourier harmonics. These harmonics can determine the elongation, irregularity and asperity of particles. Using the discrete element method, the collision of an agglomerate impacting each target particle is analysed. Several directions were selected randomly for impact to further investigate the effect of target particle orientation. The breakage of the agglomerate is observed to be largely dependent upon the local curvature at the impact point. The presence of asperities greatly changes the extent of agglomerate damage and the amount of fine particles deposited over the target. Moreover, it is shown that elongated particles can create few but large fragments upon impact, in contrast to the spherical target where collision results in smaller fragments with greater number.

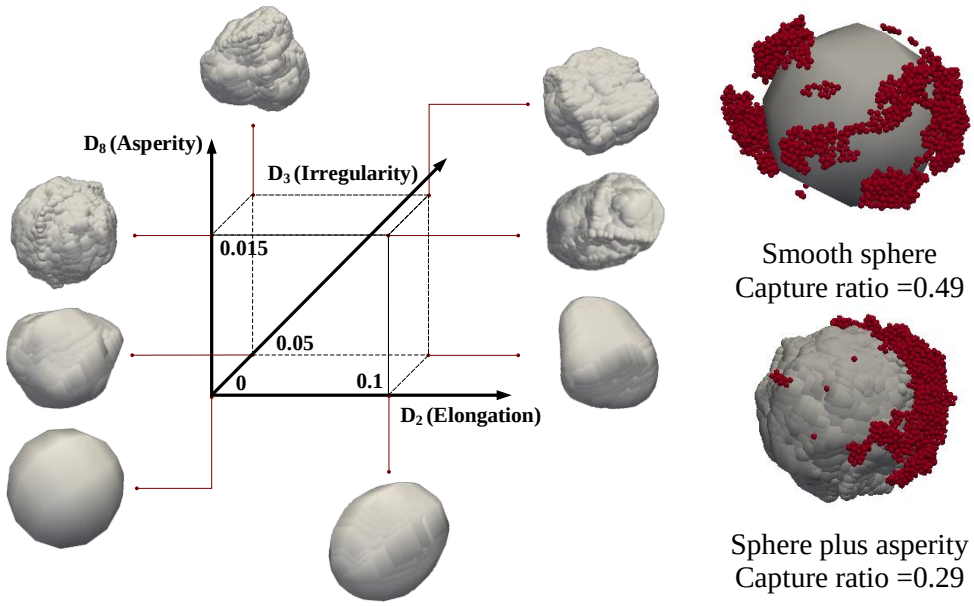

Figure 1: (Left) Generated target particles for agglomerate collision test, based on three signature Fourier descriptors, D_2, D_3, and D_8. (Right) The adhesion of fine particles depends on the surface asperities.

12. EXPLORING THE GROWTH REGIME MAP - VALIDATING THE BOUNDARY BETWEEN NUCLEATION AND INDUCTION

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The growth regime map [1] considers the granule liquid saturation, S_{max}, and the Stokes deformation number, St_{def}, as the two variables that determine the growth regime. The model ties measureable material properties (e.g. binder viscosity, wet granule strength, granule density and size) to operating conditions (e.g. impeller speed or shear rate). Increased liquid quantity will increase S_{max}. Increased impeller speed will increase the St_{def}, and potentially S_{max} dependent upon the liquid quantity, and therefore move the system from "nucleation" to "induction", or to "steady growth" and then to the "crumb" regime.

While some experimental data have been reported, validation of the regime map boundaries remains elusive. The current study presents a methodological approach for quantifying the boundary between the "nucleation" and "induction" growth regimes. The properties of the formulation are such that the "steady growth" regime is inaccessible. The nucleation regime occurs where insufficient liquid is present to achieve coalescence and only nuclei form. The induction regime occurs when strong, slowly consolidating granules do not deform sufficiently during collision. Growth occurs only with the presence of free liquid at the granule surface.

The boundary between the nucleation and induction growth regime was characterized by determining the extent of granule consolidation during the wet massing stage. Experiments were performed with liquid/solid ratios of 0.45-0.85, impeller Froude number of 0.027-0.602, and granulator scales of 10L, 65L and 600L where sample porosity was characterized at intervals during wet massing. Induction growth was observed when experimental conditions resulted in significant granule consolidation, which were visualized with the growth regime contour map in Figure 1. Differences in compactibility, disintegration and dissolution rate were observed based upon the growth regime and granule porosity.

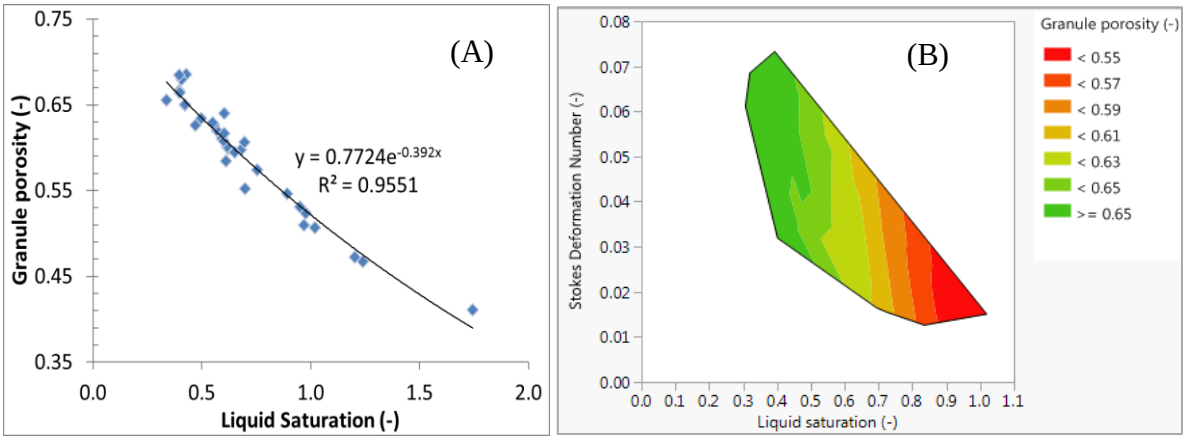

Figure 1. (A) Granule porosity as a function of liquid saturation. (B) Growth regime map depicting granule porosity contours.

[1] Iveson, S.M., Wauters, P.A.L., Forrest, S., Litster, J.D., Meesters, G.M.H., Scarlett, B., Powder Technology, 117 (2001) 83-97.

13. EXPERIMENTAL STUDY AND DEM MODELLING OF THE CONTACT BEHAVIOUR OF CYLINDRICAL PARTICLES

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In the food and pharmaceutical industry, cylindrical particles are often used and further processed in various production steps e.g. fluidization, drying and coating. In order to control and optimize these processes, the particle fluidization dynamics can be described with numerical simulations, which include computational fluid dynamics (CFD), the discrete element method (DEM) or the coupling of both methods (CFD-DEM). There are numerous CFD-DEM studies reported in the literature predicting spherical particles in complex processes, however, only few studies of fluidization processes with cylindrical particles can be found [1-3]. For cylindrical particles, there is a lack of understanding of how particle shape influences the particle contact behaviour during different loading scenarios. Especially for the exact calculation of the particle interactions in DEM, it is essential to describe the particle contact behaviour with a compatible contact model. The modelling of contact behaviour with DEM poses a number of challenges: the shape construction, the contact detection and the contact force calculation for different deformation behaviours [4, 5].

In this work, the influence of loading direction (contact geometry) and deformation behaviour (from elastic to plastic) on cylindrical particles during compression and shearing is investigated. The compression tests are performed with a Texture Analyser®. For the measurement of particle-wall sliding friction, a self-developed setup at the University of Kaiserslautern is used. During the measurement of tangential forces, the particles are fixed to a flat holder and moved over a defined wall surface at different normal loads.

The intention of these investigations is the experimental calibration of contact models, which can be applied for numerical DEM studies of fluidization processes with cylindrical particles. The behaviour of different particle shape models with the multi-sphere approach is also performed and compared with experimental results.

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[3] H. Ma, L. Xu, Y. Zhao, CFD-DEM simulation of fluidization of rod-like particles in a fluidized bed, Powder Technology 314 (2017) 355–366.

[4] S. Antonyuk, S. Heinrich, J. Tomas, N.G. Deen, M.S. van Buijtenen, J.A.M. Kuipers, Energy absorption during compression and impact of dry elastic-plastic spherical granules, Granular Matter 12 (1) (2010) 15–47.

[5] S. Antonyuk, S. Palis, S. Heinrich, Breakage behaviour of agglomerates and crystals by static loading and impact, Powder Technology 206 (1-2) (2011) 88–98.

14. SIMULATION OF CONTINUOUS SPRAY COATING IN SPOUTED BEDS USING RECURRENCE CFD

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Spray coating is an important process step in the production of many high-value products, which is commonly performed in spouted beds. Their fluid dynamics is highly complex, necessitating the use of the state-of-the-art in granular flow simulation - CFD-DEM - to guide apparatus design. This method is very computationally expense, resolving both the contact among individual particles as well as their interaction with a fluid phase. To cover the very long time scales present in industrial or even pilot scale plants, the recurrence CFD method (rCFD) [1] offers remedy: by capturing the recurrent flow patterns present in the phase dynamics and extrapolating them in a physically meaningful manner, the computational effort is minimized and the numerically cheaper transport processes can be tracked on much larger time scales.

In this work, we aim to directly predict the increase in surface coverage due to spray coating in a pilot-scale continuous spouted bed using the recurrence CFD method. Building on prior validation work on a lab-scale apparatus [2], we ran simulations on the Glatt ProCell25 plant to demonstrate the interplay of spray injection and back-mixing in a continuous apparatus.

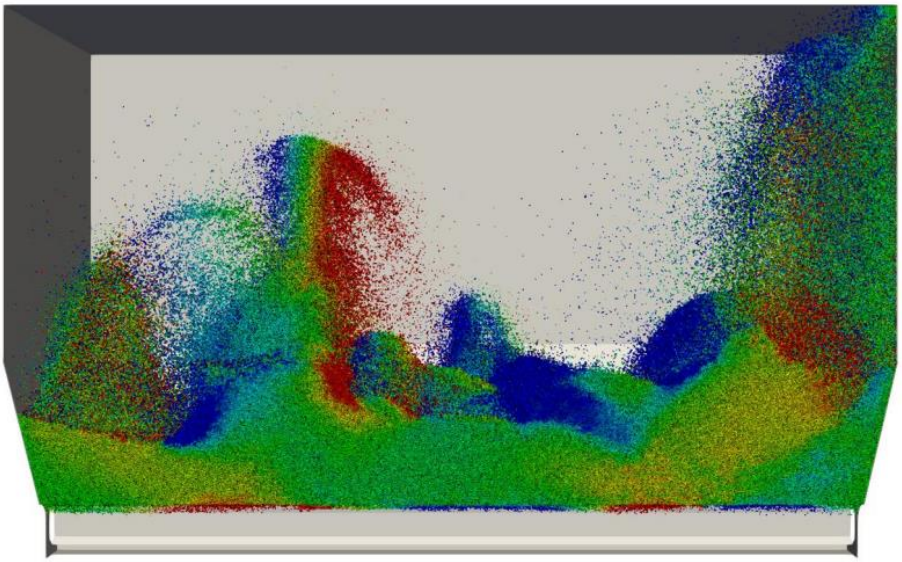

Figure 1. Particle flow in a continuous pilot-scale spouted bed containing millions of particles, simulated using the rCFD method.

[1] T. Lichtenegger, S. Pirker, Recurrence CFD—A novel approach to simulate multiphase flows with strongly separated time scales, Chemical Engineering Science, 153 (2016) 394-410.

[2] P. Kieckhefen, T. Lichtenegger, S. Pietsch, S. Pirker, S. Heinrich, Simulation of Spray Coating in a Spouted Bed using Recurrence CFD, Particuology, (2018).

15. DYNAMIC FLOWSHEET SIMULATION SYSTEM WITH ADVANCED CONSIDERATION OF THE SOLID PHASE

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The priority program of the German Research Foundation SPP-1679 "Dynamic simulation of interconnected solids processes" [1] has been established to consolidate and intensify research efforts in the area of dynamic modelling of production processes in solids processing technology. The central project of this program, presented in this contribution, is intended to develop a flowsheet simulation framework, which is able to integrate and couple the results of the entire SPP.

The developed simulation system implements a sequential-modular approach, where each unit on the flowsheet is calculated separately. To cope with the sequential simulation of flowsheets that contain recycle streams, a waveform relaxation method is applied in the system. It implies splitting of the whole simulation interval into smaller time windows, so that all units within the recycle loop can be calculated on them iteratively, and the convergence is reached much faster.

One of the main challenges related to the simulation of the solid phase is that it is usually described by distributed parameters, such as particle size, moisture content or shape. As these parameters can be interdependent, their proper processing is not a trivial task, since this interdependence should not be lost during the simulation. To overcome this problem, an approach using transformation matrices has been developed and implemented into the simulation environment. It allows correct calculation of all dependent distributed parameters, even those that are not directly considered in the particular unit.

We gratefully acknowledge financial support from the German Research Foundation (DFG) within the priority program SPP 1679 “DYNSIM-FP”.

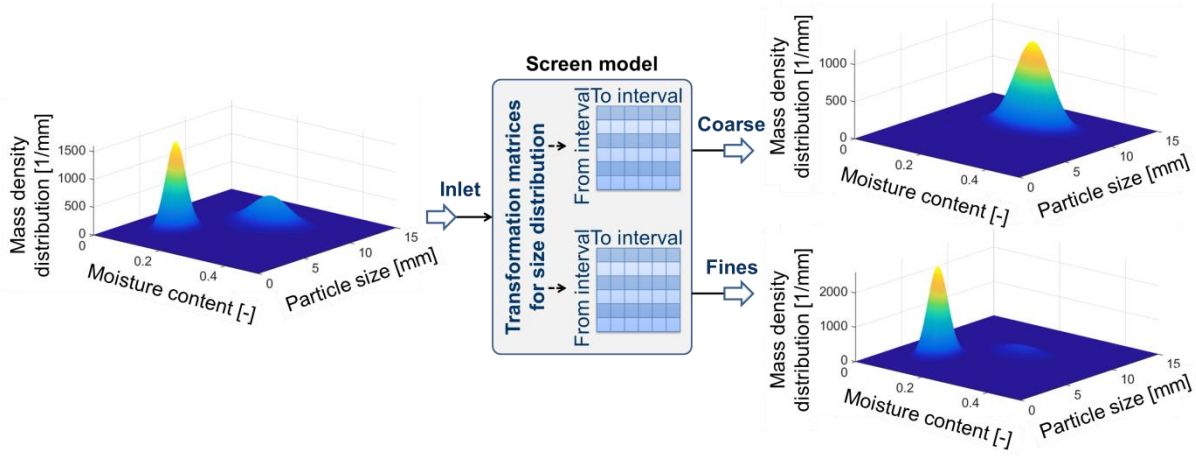

Figure 1. Example of processing interdependent multidimensional distributed parameters of solids

[1] SPP-1679: DynSim-FP, www.dynsim-fp.de (2018).

16. INTERCHANGEABILITY OF LACTOSE GRADES IN WET MANUFACTURING PROCESSES MONITORED BY DYNAMIC VAPOUR SORPTION (DVS)

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In food and pharmaceutical industries interaction of solid excipients with water is primordial for the understanding of manufacturing processes, or for the evaluation of stability and shelf life. Therein, Lactose is appreciated as cheap and functional filler-binder, which is available in various polymorphs: α-Lactose monohydrate being the most widely used form, employed as sifted, or milled grade by the majority. Commercially available spray-dried Lactose consists of crystalline α-Lactose monohydrate (approx. 85%) and its amorphous form (approx. 15%); and anhydrous Lactose carries no water of crystallization in its lattice [1].

The objective of this work was the evaluation of sorption characteristics of several commercially available lactose grades by DVS in the range of 0 - 90 % RH at 20.0°C, as water interacts at virtually all stages of manufacture. All milled and sieved materials basically show a reversible sorption classification Type II/III, indicating unrestricted multilayer formation processes and a macro-porous absorbent [2]. For spray-dried material, amorphous content induces a change in weight absorption profile between 40 and 55 % R. H., indicating bulk and surface moisture absorption, crystallization, and a subsequent desorption step. Further increase in R. H. up to 70 % results in an increase in weight which may be referred to the formation of α-Lactose monohydrate. For anhydrous Lactose, water up-take rates are comparable to sieved and milled grades, however, during desorption mass values persist at elevated levels. Overall performance of re-crystallization to α-Lactose monohydrate seems to be dependent from the materials used, impacting surfaces, formation of pores and resulting capillary effects. This limits interchangeability of Lactose grades in wet manufacturing processes.

[1] Y. D. Listiohadi, J. A. Hourigan, R. W. Sleigh, R. J. Steele, Properties of lactose and its caking behaviour, The Australian Journal of Dairy Technology, 60 (1) (2005) 33 - 51.

[2] M. Kruk, M. Jaroniec, Gas Adsorption Characterization of Ordered Organic-Inorganic Nanocomposite Materials: a review, Chem. Mater., 13 (10) (2001) 3169-3183.

17. INFLUENCE OF POLYDISPERSITY AND NON-SPHERICITY OF PARTICLES ON THE STABILITY OF A THREE-DIMENSIONAL PRISMATIC SPOUTED BED

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Spouted beds haven shown great applicability for the fluidization of particles, which are difficult to handle in fluidized beds, as e.g. very small or big, cohesive or non-spherical ones. The particles are accelerated by the high gas velocities in the spout and fall along the walls back into the annulus zone resulting in a fountain-like flow pattern. The stability of the spouting behaviour can be identified by visual observations in the form of variations in bed expansion height or spout deflections and by analysis of the pressure drop fluctuations. Former investigations on prismatic spouted beds were focused on the characterization of the flow dynamic of monodisperse systems (e.g. [1]). In industrial relevant processes, as e.g. agglomeration, granulation or coating, systems with particle size distributions are used. Therefore, the purpose of this study was the determination of the influence of different sized γ-Al_2O_3 particles (0.6, 1.8 and 3.0 mm) as well as the application of particles with similar size but different density or shape.

Experiments were performed with different concentrations and gas volume flow rates in a transparent replica of the laboratory spouted bed ProCell 5 (Glatt GmbH, Germany). Stability was quantified by analysis of the pressure drop fluctuations with Fourier Transform (FFT). It was found that the stability range of the coarse particle fraction and its interval size are decreased when adding finer particles. Small particles in binary and ternary mixtures were mainly detected near the apparatus' walls, whereas the bigger ones resided in the centre (Figure 1). This segregation is disadvantageous when performing granulation experiments with centred nozzles as the already coarse particles will further grow while the growth of the smaller ones is inhibited. In addition, it was observed that the stability range of particles is decreased when using particles of almost the same size but with a non-spherical shape.

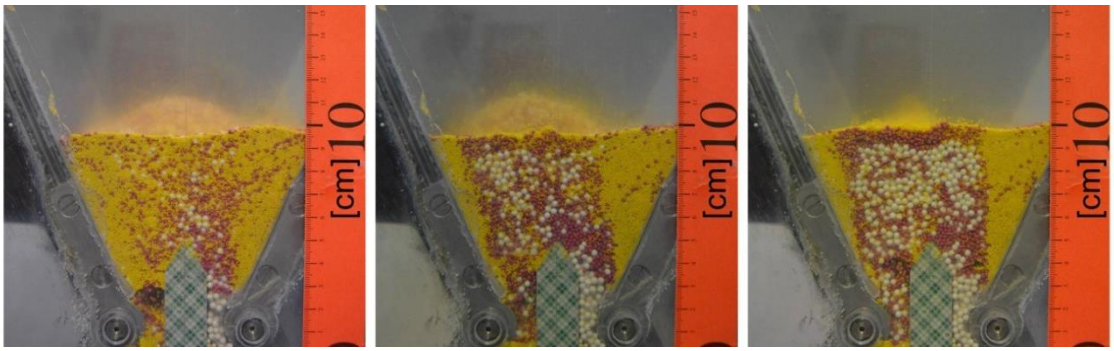

Figure 1. Snapshots of segregation effects observed with a ternary particle mixture. Time interval between images is 60 s. 20 wt.-% 0.6 mm (yellow), 20 wt.-% 1.8 mm (red) and 60 wt.-% 3.0 mm (white) γ-Al_2O_3 particles; gas volume flow rate: 50 m^3/h.

[1] V. Salikov, S. Antonyuk, S. Heinrich, V.S. Sutkar, N.G. Deen, J.A.M. Kuipers, Characterization and CFD-DEM modelling of a prismatic spouted bed, Powder Technology, 270 (2015) 622–636.

18. IN-LINE MONITIORING OF COATING LAYER THICKNESS IN A SPOUTED BED VIA OPTICAL COHERENCE TOMGRAPHY

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Particle coating is widely used in various industries, as e.g. for food, detergents and fertilizer processing or in pharmaceutical applications. The main challenge is the formation of a homogeneous layer without cracks to protect the core material from the environment. Often, the coating is applied on active substances like pharmaceutical ingredients or enzymes, which should be released only under defined conditions. Spouted beds have shown great applicability for coating processes as the particle movement is more structured than in fluidized beds and heat, mass and momentum transfer are improved due to the fountain shaped fluidization [1]. Besides the homogeneous distribution on the scale of one single particle, the homogeneous coating of the entire particle bed in one production charge is a criterion of quality. The in-line coating layer measurement is advantageous compared to off-line methods because real-time data are available and the process is not disturbed.

Optical coherence tomography (OCT) was applied for in-line measurement of the coating layer thickness. The method is an interferometric approach, which makes use of the coherence properties of light in order to obtain depth profiles of investigated semi-transparent and turbid materials in a contactless and non-destructive way [2]. Coating experiments were performed in the laboratory spouted bed ProCell 5 (Glatt GmbH, Germany). The obtained values from OCT images were validated by off-line measurements (e.g. µ-CT). It is shown that OCT enables the correct layer thickness measurement on the scale of single particles. High variations were observed, which are probably caused by an inhomogeneous distribution of droplets on the particle surface or an insufficient spreading of those.

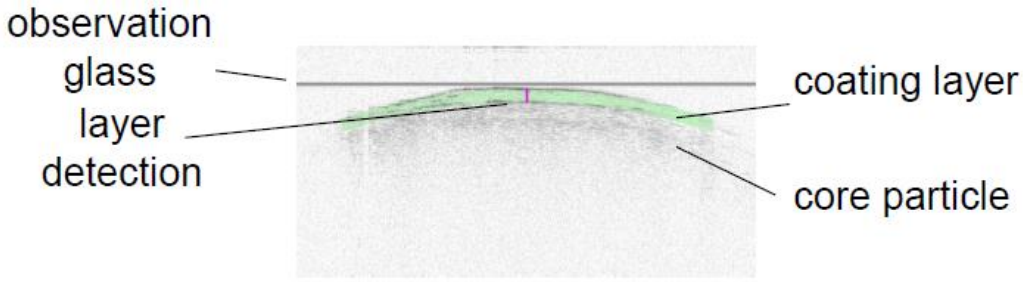

Figure 1. Exemplary coating layer measurement obtained by in-line OCT analysis.

[1] N. Epstein, J.R. Grace (Eds.), Spouted and spout-fluid beds: Fundamentals and applications. Heat and mass transfer, Cambridge University Press, Cambridge, New York, 2011.

[2] D.M. Koller, G. Hannesschläger, M. Leitner, J.G. Khinast, Non-destructive analysis of tablet coatings with optical coherence tomography, European Journal of Pharmaceutical Sciences, 44 (1-2) (2011) 142–148.

19. WETTING OF SOLUBLE AND HETEROGENEOUS POWDERS

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Wetting is the first step during food powder reconstitution and strongly depends on the interactions of the liquid and the surface of the wetted particle, expressed by the contact angle. Due to the heterogeneous composition of food materials in terms of hydrophilic and hydrophobic components on the particle surface, also the wetting process is of heterogeneous nature. While a hydrophilic surface favours the wetting process with water, the contact of a hydrophobic surface with water slows down the wetting performance. Furthermore, the solubility of food ingredients, such as sugars, increases the complexity of understanding and describing the wettability.

Thus, we studied the liquid penetration into model food powders consisting of a stochastic distribution of hydrophilic, soluble and hydrophobic, inert particles using a Washburn setup (K100 tensiometer, Krüss). Soluble sucrose and sodium chloride powders were used as hydrophilic food components and silanized and shellac coated glass beads were prepared as hydrophobic, inert material. All powdered materials were characterized in terms of their contact angles and powder properties. Different mixtures of hydrophilic powders with hydrophobic glass beads were produced and their penetration rates were determined. For predicting the liquid penetration, a model for water penetration into food powders was developed considering solute concentration dependent liquid properties. The model is based on the solution of a coupled system of two differential equations representing capillary rise into a pore network and the mass transfer equation. Viscosity was found to have a major influence on the wetting kinetics if sucrose was involved. In case of sodium chloride mixtures, the change of pore network properties due to dissolution played a major role. Our model predicts penetration rates which are close to the experimental data. Thus, we conclude that it is suitable for predicting the capillary penetration into food powders consisting of hydrophilic, soluble and hydrophobic, inert particles.

20. GRANULATION OF WET GRANULAR MEDIUM IN ROTATING DRUM

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In this work, we study the agglomeration process of wet granular materials in rotating drum. Agglomeration of fine particles is used in many industrial processes such as powder metallurgy, iron-making industry, food and pharmaceutical industries. Fine granular materials are prepared and mixed in required proportions, compacted into a granule or tablet and finally sintered to acquire sufficient mechanical strength and toughness needed for subsequent operations. We present a numerical model for the agglomeration of wet particles in rotating drum [1, 2]. The particles interact through capillary liquid bridges, which are modeled by accounting for the cohesive and viscous forces expressed analytically as a function of different parameters such as the distance between primary particles, liquid volume and viscosity, surface tension and particle sizes. The model also assumes that the liquid is transported by the primary particles modeled as agglomerates of fine particles. We find that this model is able to simulate the granulation of particles in a rotating drum in which a given amount of liquid is homogeneously re-distributed. Our simulations show that the granule size increases exponentially with the number of drum rotations and in proportion to the amount of liquid. We investigate the effects of process and material parameters such as particle size distribution, mean particle size, friction coefficient between the primary particles and liquid viscosity in each agglomeration process.

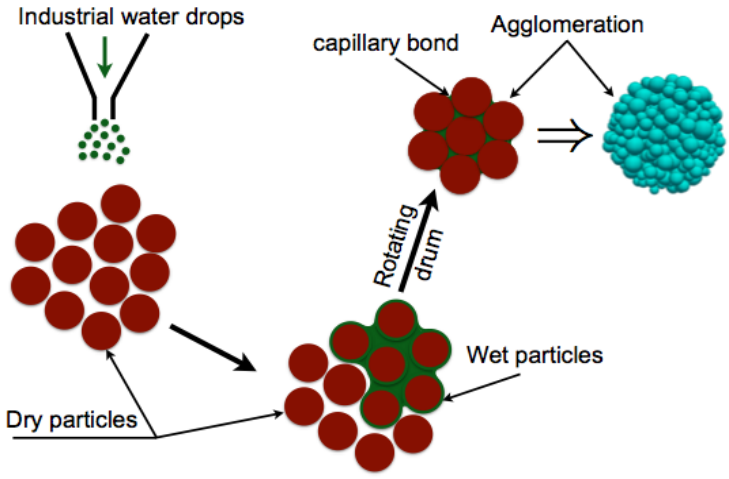

Figure 1. Mechanism of wet agglomerate formation

[1] T-Trung. Vo, P. Mutabaruka, J-Y. Delenne, S. Nezamabadi, F. Radjai, Strength of wet agglomerates of spherical particles: effects of friction and size distribution, European Physical Journal 140 (2017) 08021.

[2] T-Trung. Vo, P. Mutabaruka, S. Nezamabadi, J.Y. Delenne, E. Izard, R. Pellenq, F. Radjai, Mechanical strength of wet particle agglomerates, Mechanics Research Communications 92 (2018) 1-7.

21. SCALING UP A CONTINOUS WET TWIN-SCREW GRANULATION PROCESS

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How to increase the amount of product made in a continuous process? There are several possibilities to do this: Staying on the same scale of equipment (scale-out) either the production time or the throughput can be increased. Of cause there is a natural limit in every kind of granulation machine. Therefore, a scale-up to larger equipment is needed.

In this work, a scale-out and a scale-up case study is shown where a placebo formulation is granulated on a lab-scale machine (Thermo Scientific® Pharma 11) at different throughputs and on a production-scale machine (Thermo Scientific® Pharma 16). The results show the critical process parameters to operate, scale-out and scale-up the process. Those include the filling level of the screws as reported before [1], [2]. In addition to that the mean residence time of the material within the twin-screw needs to be considered. As can be seen in the picture below, if the crucial parameters are considered in a scale-up process comparable particles are produced on both scales. The granule quality produced on a small scale is predictive for granule quality obtained on a larger scale. This concept has also been proved for continuous wet granulation including the drying process (Glatt® MODCOS xs-line with 11 mm screws, s-line with 16 mm screws and m-line with 24 mm screws).

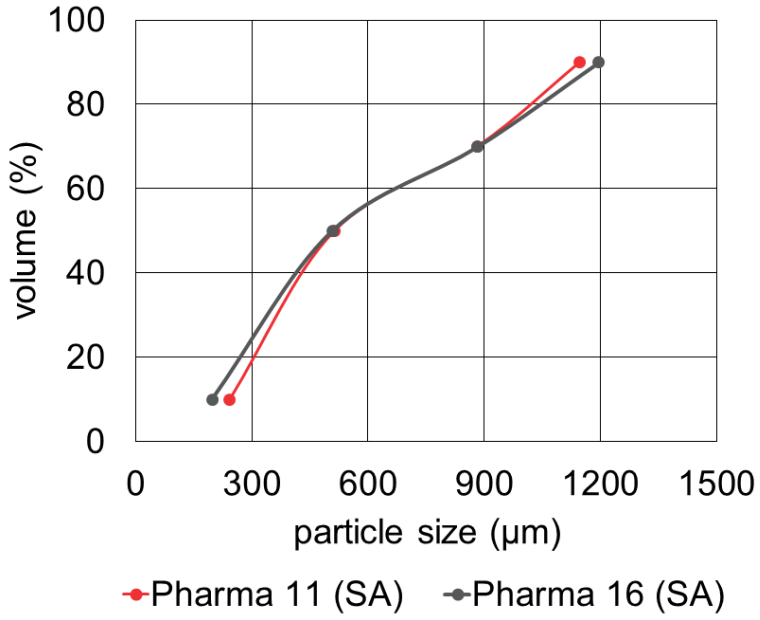

Figure 1. Particle size distribution from sieve analysis (SA)

[1] A. Kumar et al., “Mixing and transport during pharmaceutical twin-screw wet granulation: Experimental analysis via chemical imaging,” Eur. J. Pharm. Biopharm., 87, no. 2 (2014) 279–289.

[2] T. C. Seem et al., “Twin screw granulation - A literature review,” Powder Technology., 276 (815) (2015) 89–102.

22. TSG - AN UNDERESTIMATED TECHNOLOGY FOR PHARMACEUTICAL DEVELOPMENT

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Granulation is and will be an important intermediate process step in pharmaceutical manufacturing. There are versatile technologies to perform granulation, i.e. increase particle size and efficiently blend ingredients of a formulation. Twin-screw granulation (TSG) gained attention in the recent years. In most cases this relates to a wet granulation where water is used to perform the granulation. But the twin-screw technology enables the operator to perform a variety of processes. A dry or melt granulation can be done as well as wet-extrusion spheronization. Thus, using one machine different types of granulation processes can be tested to find the optimum for a defined formulation. This makes a twin-screw technology a valuable tool in pharmaceutical research and development. The picture below shows an overview on twin-screw processes and typical pellets and granules. In this work, different case studies are summarized including a literature review on the different granulation technologies. Advantages and disadvantages, formulation requirements and critical process parameters are reviewed to build a solid base for galenic development.

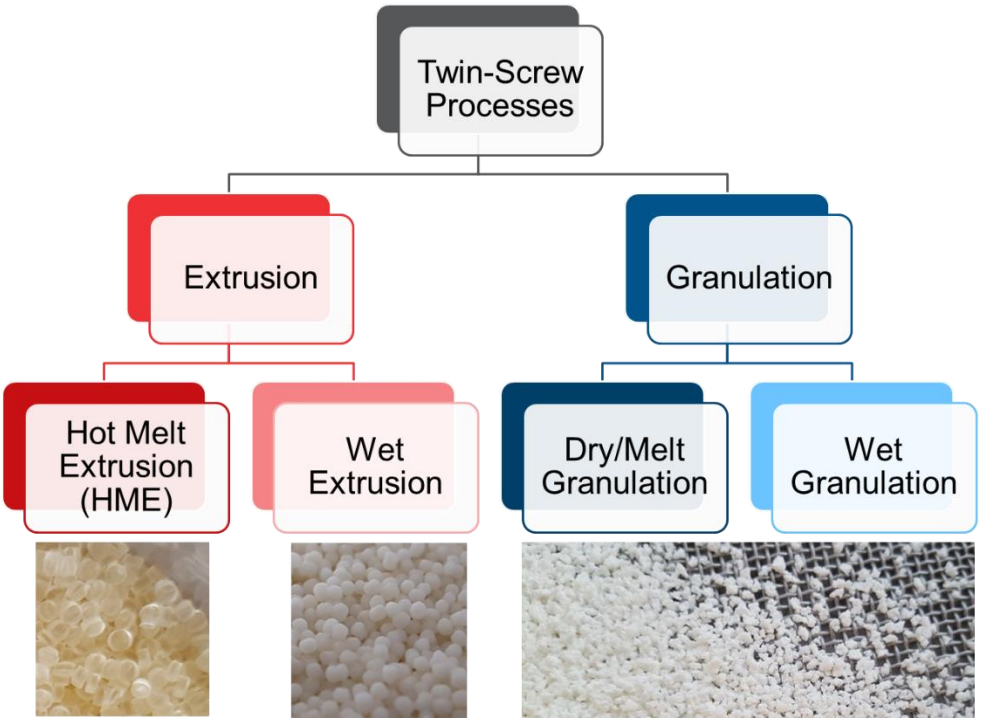

Figure 1. Summary of pharmaceutical twin-screw processes

23. STRUCTURE ANALYSIS OF SODIUM BENZOATE LAYERS FROM DRYED DEPOSITED DROPLETS

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Most coatings are produced by consecutive applying and drying of solutions or suspensions on the substrate. However, the focus of this project was processes which make use of constant and simultaneous spraying and drying. This kind of processing is typical for continuous fluidized bed coating [1]. Such coating procedures showed a strong dependence of the coating layers on drying conditions in previous experiments, as it is shown in the subsequent figure. Therefore, analyses of the incrementally resulting structures from sessile droplets dried under various conditions are expected to contribute to the understanding of the more complex processes within a fluidized bed [2].

In the course of this project, the layer structure resulting from drying of deposited sodium benzoate solution droplets was analysed in a droplet-by-droplet manner. This was done by applying droplets of various sizes from the micro- to nanoliter range on a glass surface. After application, the sessile droplets were dried under varying conditions up to technical. The resulting porosity as well as layer and droplet residue structure were measured incrementally during layer build-up by means of white-light interferometry.

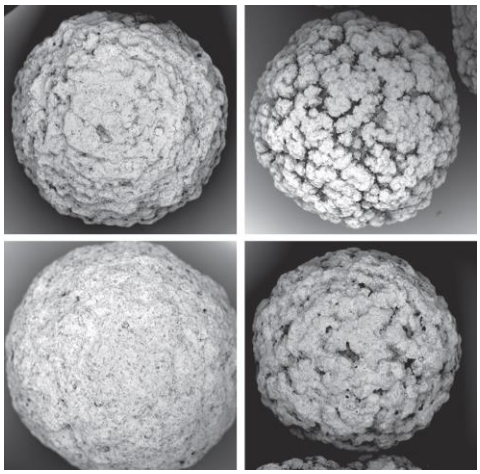

Figure 1. Images of glass beads coated with NaB under varying drying conditions [3]

[1] S. Heinrich, M. Peglow, M. Ihlow, M. Henneberg, L. Mörl, Analysis of the start-up process in continuous fluidized bed spray granulation by population balance modelling, Chem. Eng. Sci., 57 (2002) 4369-4390.

[2] F. Sondey, M. Peglow, A. Bück, E. Tsotsas, Experimental investigation of the morphology of salt deposits from drying sessile droplets by white-light interferometry, AIChE J., 64 (2018) 2002-2016

[3] C. Riek, T. Hoffmann, A. Bück, M. Peglow, E. Tsotsas, Influence of drying conditions on layer porosity in fluidized bed spray granulation, Powder Technology., 272 (2015) 120-131

24. MODELLING THE COMPACTION BEHAVIOR OF COHESIVE MATERIALS IN DRY GRANULATION PROCESS USING DEM

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Roll compaction is a critical step in the dry granulation process of powders as both strength and density of the ribbon determines the particle size distribution of the final granular product. To develop a complete process control unit of dry granulation, there is a need for a computational model of the compaction process to predict the final products properties. The state of the art describes roll compaction, or rather the ribbons properties, via analytical 1D models and numerically via multi-dimensional finite element method models. Analytical models show inaccuracies in the properties-distribution of the ribbon as inhomogeneities are neglected. Finite element models represent the particle behavior as a powder mass continuum. This introduces problems when considering ribbon breakage in later process steps of dry granulation. To represent the compaction behavior of cohesive powders via DEM correctly, there is a need for a calibration model to fit contact model parameters. Additionally, the frictional coefficients must be adapted to the raw material.

In this work, a workflow to calibrate DEM contact model parameters describing powder compaction in roll compaction process is presented. The focus for this process is placed in accurately describing cohesion/compaction and frictional effects. Thus, a pressure-density-relationship is derived from die compaction experiments. In DEM, the contact model parameters are modified for the purpose to fit the experimental behavior regarding pressure-density. The rolling friction coefficient is calibrated using the angle of repose experiment. Subsequently, these parameters are used to predict the final density during roll compaction process to validate the predictability of the calibration model by comparing with the real ribbon density.

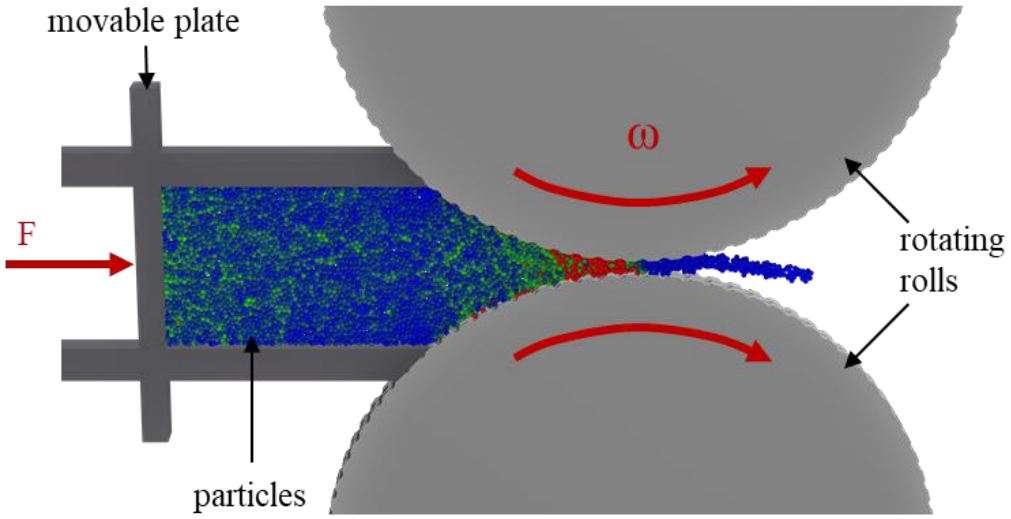

Figure 1. Contact forces experienced by particles during the roll compaction process.

25. EXPERIMENTAL INVESTIGATION OF PROCESS BEHAVIOR OF CONTINUOUS FLUIDIZED BED SPRAY AGGLOMERATION WITH INTERNAL CLASSIFICATION

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Agglomeration is a particle formulation process in which at least two primary particles are combined to generate a new one. The agglomerates can be formed in different equipment, for example drums, pans or in fluidized beds. In case of fluidized bed spray agglomeration, a solid-contained liquid, called binder, is sprayed on the particles. The binder can be a solution, suspension or melt. The principle of fluidized bed spray agglomeration is especially used in chemical, food and pharmaceutical industry [1]. The advantages are good mixing and uniform high heat and mass transfer rates between particle, liquid and gas phase. Compared to previous batch processes the additional benefits of continuous processing are a constant product quality and higher throughputs. Based on operating disturbances, the behaviour and due to this the product quality of the agglomerates can change.

The goal of the present work is an experimental investigation of spray agglomeration operating in continuous mode in a cylindrical fluidized bed with internal separation. The investigation contains influences of operating disturbances, like abrupt changes in feed rate or spray rate. Especially, the related dynamic changes in process behaviour and product quality [2] will be observed and analysed. The starting materials for fluidized bed and continuous feeding during the process are glass spheres. The binder is a solution of water and hydroxylmethylcellulose (HPMC). Particles having the target size are continuously discharged through a classifying tube, which is centrally installed at the bottom of the fluidized bed. The experimental results will be compared with a developed population balance model (PBM) [3].

[1] Bück, A., Tsotsas, E., Encyclopedia of Food and Health. Vol.1. Oxford: Academic Press, Ch. Agglomeration, (2016) pp. 73 – 81.

[2] Dadkhah, M., Peglow, M., Tsotsas, E.,. Characterization of the internal morphology of agglomerates produced in a spray fluidized bed by X-ray tomography, Powder Technology 228 (2012) 349 – 358.

[3] Golovin, I., Strenzke, G., Wegner, M., Palis, S., Bück, A., Kienle, A., Tsotsas, E.,. “Parameter identification for continuous fluidized bed spray agglomeration”, 6th International Conference on Population Balance Modelling – (2018) PBM (Ghent)

26. EXPERIMENTAL INVESTIGATION OF PARTICLE DISPERSION IN CONTINUOUS SPRAY AGGLOMERATION PROCESS IN A HORIZONTAL FLUIDIZED BED

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Spray fluidized bed agglomeration process is a size enlargement process widely used in chemical, pharmaceutical and food industry to enhance properties of powders such as size, flow behavior, rewettability and density. There are two process options: the batch and the continuous process. Compare to batch operation, the continuous process holds serval advantages such as low labor, low downtime and high product throughput. But because of the continuous feed and discharge of particles, dispersion appears, causing a distribution in residence time and hence in particle properties.

Therefore, this work deals with the measurement and control of particle residence time distribution in the spray agglomeration process achieved a horizontal fluidized bed. In this study, a continuously-operated pilot horizontal fluidized bed (GF/Procell 20 from Glatt GmbH) is employed. The process is conducted with glass beads and water-based binder hydroxypropylmethylcellulose (HPMC). To characterize the residence time distribution (RTD) of particles, glass beads coated with sodium benzoate are used as tracers. Different sizes of glass beads and variable operation parameters such as fluidization air speed, air temperature, binder spray rate, outlet weir heights and different configurations of internal baffles are used. In the process, the steady state is reached and samples are taken periodically at the outlet. By characterizing the conductivity of samples, the tracer concentration vs. time is achieved and analyzed by different methods such as tank-in-series model, the method of moments and dispersion model [1] and then compared with some existing correlations [2, 3].

[1] P. Bachmann, E. Tsotsas, Analysis of residence time distribution data in horizontal fluidized beds, Procedia Eng. 102 (2015) 790–798.

[2] P. Bachmann, A. Bück, E. Tsotsas, Investigation of the residence time behavior of particulate products and correlation for the Bodenstein number in horizontal fluidized beds, Powder Technol. 301 (2016) 1067–1076.

[3] L. Nilsson, R. Wimmerstedt, Residence time distribution and particle dispersion in a longitudinal-flow fluidized bed. Chemical Engineering Science, 43 (5) (1988) 1153-1160.

27. PREDICTION OF THE GROWTH KINETICS AND AGGLOMERATION MECHANISMS USING A MIXER TORQUE RHEOMETER

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The evolution of a high shear wet granulation process (HSWG) depends on wet masses properties such as strength and deformation. In literature granule growth is described in terms of Stokes deformation number (St_{def}) using the growth regime map [1] but also evaluating the material exchange as proposed by Bouwman et al. [2]. The purpose of this study was to evaluate the ability of a mixer torque rheometer (MTR3, Caleva, UK) to predict the growth kinetic and the agglomeration mechanism of granules produced by HSWG. For this study three formulations were selected, the first composed of 100% (w/w) of microcrystalline cellulose (MCC100%), the second constisting in a mixture 1:1 of sucrose and microcrystalline cellulose (SUCR50%) and the third containing 5% (w/w) of xanthan gum and 95% (w/w) of microcrystalline cellulose (XG5%). The MTR3 was initially used to identify the water amount necessary for the HSWG. Afterwards MTR3 was employed to evaluate the evolution of the wet mass torque over the time in order to identify the torque peak and to study the influence of different parameters (L/S, shaft speed and binder flow rate) on this value. The maximum torque peak developed by the wet masses could represent a measure of the wet granules strength and it is inversely proportional to St_{def}. Thus, this value can be useful in the prediction of the granule growth mechanism. In particular, high torque peak values correspond to the induction growth, low torque peak values correspond to crumb growth and finally intermediate torque peak values correspond to the steady growth mechanism. MTR3 measurements showed that formulations MCC100% and SUCR50% present a steady growth regime, instead XG5% shows an induction growth mechanism for all the conditions analyzed. Moreover, for SUCR50% the toque peak values are strongly dependent on experimental conditions and consequently a change in the growth could be observed. Granulation experiments were then performed in a lab scale high-shear mixer (Rotolab, IMA Zanchetta, Italy) in order to verify the growth kinetics and the growth mechanisms by evaluating also the material exchange [2]. Granulation experiments confirmed the mechanisms predicted by the rheological tests, and in particular for the SUCR50% it was possible to observe that the growth kinetic is correlated to the torque peak values and depends on impeller speed and water amount. In conclusion the rheological characterization of wet masses could represent a tool to predict the growth of granules during the granulation process.

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[2] A.M. Bouwman, M.R. Visser, G.M.H. Meesters, H.W. Frijlink, The use of Stokes deformation number as a predictive tool for material exchange behaviour of granules in the ‘equilibrium phase’ in high shear granulation, International Journal of Pharmaceutics 318 (2006) 78–85.

28. GRANULE CHARACTERISATION AFTER TWIN SCREW GRANULATION

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Within the pharmaceutical industry, a shift towards continuous processing of granules via wet granulation, away from traditional batch-wise techniques is underway. Twin Screw Granulation (TSG) is a continuous process which, in recent years, has been the subject of much research to increase knowledge in its role within solid oral dosage form manufacturing. Further work is required to gain a deep understanding of the mechanisms and process factors required to predict the characteristics and quality of the resulting granules required by the FDA regulations, for example Quality by Design (QbD) and Process Analytical Technology (PAT).

This study presents the key properties of granules produced via TSG including particle size distribution, shape, internal porosity, strength and tabletabilty. Granules of pure mannitol and two varieties of lactose were produced using TSG with water as a liquid binder. The TSG set-up was varied from conveying only elements, one kneading zone and finally two kneading zones.

Granule size was found using sieve analysis and increased dramatically with increasing liquid content and kneading zones used within the TSG barrel. Utilising bulk uniaxial compaction and micro X-ray computer tomography as characterisation techniques, the granules produced at a high liquid to solid ratio were found to be stronger and less porous than those with low liquid content across all three materials. A hydraulic Compaction Simulator was used to assess the granule tabletability and results showed that the compressive nature of granules varied between all materials and manufacturing conditions.

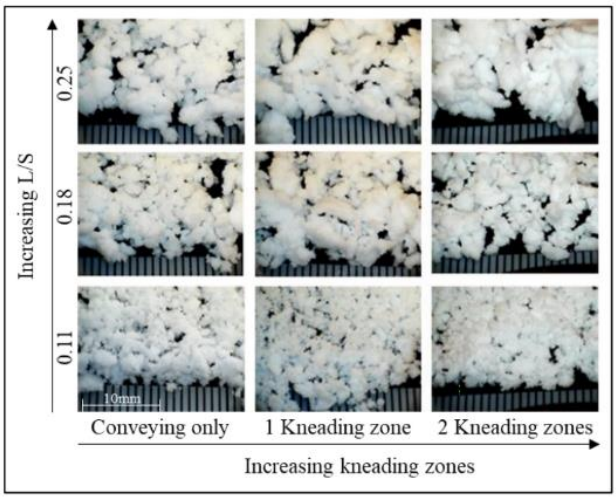

Figure 1. The effect of increasing granulating fluid and TSG kneading zones on mannitol granule size.

29. SCALE-UP INVESTIGATIONS OF TABLETING PROCESSES FROM LAB TO PRODUCTION SCALE

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Tableting is an important production process in various industries, such as the chemical and the pharmaceutical industry. Formulation and rough process parameter estimate for novel products are usually carried out on lab scale with only small material demands, commonly using eccentric presses. The transferability from this lab scale to production scale using rotary tablet presses is often limited by differences in the construction resulting in variations in sub-processes of differently scaled tablet presses. This impairment usually results in altered tablet properties (uniformity of mass, homogeneity, mechanical strength) or even the occurrence of tableting problems (capping, sticking, filling deficiencies) which were unforeseen at lab scale. Due to the complexity of powder behaviour in handling processes in general and in a tableting machine in particular, no standardized procedure for process scaling from lab to production scale is available, yet. This often results in high time and cost investments during feasibility studies for new materials. This study aims to identify critical process and material parameters affecting the transferability and to derive scale-up rules, which are applicable for a wide range of products.

The tableting process can be divided into five stages, which affect the structural and mechanical properties of tablets: powder feeding, die filling, compression, decompression, and tablet ejection. This study focused on the stages of compression and decompression by systematically varying the dwell time, compression speed and compaction stresses. The influence of varied process parameters on the structural and mechanical properties of tablets was characterized by determining tablet porosity and tensile strength. In-die measurements of force-displacement curves were evaluated to gain insight into the compression behavior at different compression profiles, (quick) elastic recovery, and energies spent.

Investigated materials included untreated, wet and dry granulated catalysts and detergents, which covered a wide range of different compression and compaction behaviour. Experiments were carried out using the compaction simulator Styl'One Evolution on lab scale, the rotary tablet press XL100 on pilot scale and the rotary tablet press XL 400 on production scale. A generic compression profile of the compaction simulator was utilized to characterize fundamental process parameter-dependent deformation behaviour of materials. In addition, the compression profile was customized to simulate that of the rotary tablet presses for varying process parameters, simulating varying compaction stresses and die table velocities.

Die filling and applied compression profile were identified as critical process steps directly affecting the scalability of the tableting process. The application of the compaction simulator on lab scale enabled the simulation of compression profiles of rotary tablet presses on pilot and production scale resulting in a more reliable and faster scale-up and facilitating a faster and cost-reduced development of new tablet formulations.

30. EFFECT OF PROCESS PARAMETERS ON GRANULATION OF ALUMINA POWDERS

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Alumina (Al2O3) powder has received a lot of attention amongst engineering materials due to its widespread use in the fields of electronics, catalyst supports and high temperature applications. The powder needs to be agglomerated for ease of handling and for improved flowability and performance. Early studies on granulation of alumina powders involved partial pre-wetting of the powder, followed by granulation in a fluidized bed granulator [1]. Currently, freeze granulation and spray drying are used for producing granules of alumina [2, 3]. The scalability of these processes, however, is an issue. In this work, we explored the feasibility of producing granules of alumina using scalable granulation equipment like the Loedige ploughshare mixer. Disc pelletizer, another agglomeration equipment used widely in materials and pharmaceutical industries, was also explored for this purpose.

In a ploughshare mixer, granulation is facilitated by a plough shaped tool that mixes the sample powder in the presence of the binder. A 'chopper' placed close to the wall helps in the breakdown of larger granules [4]. The effects of various process parameters such as the speeds of the plough and the chopper, time of granulation, amount and concentration of the binder, and initial feed size distribution on the size and shape of the alumina granules, were studied in a laboratory scale ploughshare mixer using polyvinyl alcohol solution as the binder. Similar studies were also carried out using the disc pelletizer. The particle shape and size distribution of granules were determined using image analysis and a particle size analyzer, respectively. Smaller granules were produced in the ploughshare mixer as compared to the disc pelletizer. Interestingly, a bimodal particle size distribution was obtained with both the devices. These results are of value in the scale-up of the equipment and in converting the batch process into a continuous process.

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[4] P. W. Cleary, J. E. Hilton, M. D. Sinnot, Modelling of industrial particle and multiphase flows, Powder technology, 314 (2017) 232-252.

31. MECHANISTIC UNDERSTANDING OF HYDROPHOBICITY ON BI-COMPONENT HIGH SHEAR WET GRANULATION GROWTH KINETICS

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To achieve enhanced process understanding of granulation of two or more components, it is important to develop a more mechanistic understanding of the process that in turn can quantify the effect of material properties, process parameters, and equipment design parameters on granule properties. The inability to predict the effect of raw material composition (e.g., during a formulation ruggedness study) in granulation is a limitation of available aggregation kernels. Developing such a model that could predict granule product attributes based on the individual raw material properties and composition will significantly help to improve the product/process development timelines. The purpose of this work is to establish a combined experimental and computational approach for developing a composition dependent bi-component aggregation kernel that could assist in studying the impact of raw material properties on final granule attributes.

In the presented work, the role of understanding material properties was evaluated based on the granule size distribution (GSD) data obtained from high shear wet granulation of ibuprofen-USP (API) and microcrystalline cellulose (MCC-101) (excipient) under fixed operating conditions and design parameters. Further studies were performed to prove or disprove three potential hypotheses (H) on the effect of bicomponent formulation on GSD. The reason for increase in GSD (H1) is due to the deformability of API, (H2) is due to the difference in contact angle of two components with the binder liquid, and (H3) is due to the maximum pore saturation of constituent materials or any combination of the above hypotheses. These hypotheses were tested by performing high shear wet granulation using a set of materials (Ibuprofen, MCC-101 and acetaminophen). Efforts were made to reproduce these findings by developing a bi-component population balance model that leverages theory from existing kernels in the literature, which specifically is a function of individual material contact angle, maximum material pore saturation and material yield strength for two components. The comparison of the simulated PBM with experimental results is expected to confirm the validity of the aggregation kernel in a high shear wet granulation process.

32. APPLICATIONS OF MECHANISTIC MODELS FOR INDUSTRIAL WET GRANULATION PROCESSES: DATA REQUIREMENTS, BEST PRACTICES, AND TYPICAL WORKFLOWS

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The past decade has brought significant advances in quantifying the mechanistic understanding of wet granulation processes through population balance models, regime map approaches, and discrete element modelling. In previous work, a unifying framework for modelling wet granulation processes was presented, considering the mechanistic differences between high shear, twin screw, and fluid bed granulation processes [1]. Despite this progress, the application of these models to describe real processes and solve problems encountered in industry has lagged behind. Model validation techniques have not been well established, and the large number of unknown parameters poses challenges around data requirements and calibration techniques.

In this work, typical use-cases for mechanistic models will be discussed, including process design, scale-up, risk mitigation, and control. Workflows for model validation will be presented for each case, including model discrimination and experimental data requirements. Collection and treatment of particle size distribution data will be explored, along with the relative importance of other measures of granule attributes, such liquid distribution and porosity. Best practices with respect to data analysis, model calibration, and blind testing will be identified. Post-validation activities will also be discussed, including process optimisation, risk assessment through global sensitivity analysis, and design space exploration. Industrial case studies will demonstrate these concepts for twin screw and high shear wet granulation processes.

[1] D. Barrasso, D. Slade, J.D. Litster, S.K. Bermingham, A unified framework for mechanistic model development and validation of high shear, fluid bed, and twin screw wet granulation processes, Presented at AIChE, San Francisco, November 2016.

33. CATCH ME IF YOU CAN - AUTOMATIC DETECTION OF SCORCHED OR OTHER FOREIGN PARTICLES IN GRANULATION PROCESS USING INLINE PROBES

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Granulation, the process of particle enlargement by agglomeration technique, is one of the most significant unit operations in the production of pharmaceutical, chemical or food products. These process transforms fine powders into free-flowing, dust-free granules that are easy to compress. Nevertheless, granulation poses numerous challenges due to high quality requirement of the formed granules in terms of content uniformity and physicochemical properties such as granule size, bulk density, porosity, hardness, moisture, compressibility, nonexistence of foreign particles etc. together with physical and chemical stability of the drug, the chemical component or food ingredient.

Realtime monitoring of the named parameters using inline measurement technologies was discussed in general but not implemented throughout the industrial community due to severe technical challenges. Especially the measurement of granule size, granule shape and colour (implying scorched or other foreign particles) has not been implemented successfully in industrial granulation processes. The presentation will give a brief overview of existing measurement techniques developed for the above mentioned tasks, as different techniques based on different physical principles for measuring particle size distributions are available. The authors did compare several measurement techniques and will provide those results.

The mainly used system for this presentation is an photo optical in-line measurement technology combined with an innovative image processing and analysis software. These analyzes show exactly the size, shape and colour of the granules. Additional parameters like local concentration or moisture can be derived from the image analysis. This makes it possible to monitor and to optimize granulation processes in a feedback loop, as the particle data are available in real time.

The quality and variability in quality of the images obtained by the camera computer system (see Figure 1) greatly influences the success of the automated interpretation. All important step will be discussed and presented in detail. A first example is given in the following figure.

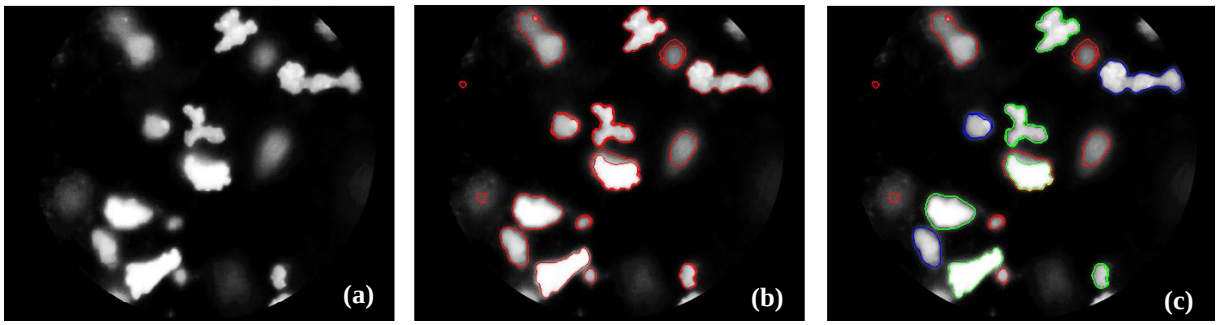

Figure 1. image analysis steps for irregular shaped particles: (a) – original image; (b) – segmented image; (c) – classified image; only classified particles are used for the size distribution (green and blue; red are excluded)

34. FLUIDIZED BED GRANULES CONTAINING POLYMERIC NANOCAPSULES: GRANULES GROWTH BEHAVIOUR

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Recently polymeric nanocapsules were reported as a binder system to produce fluid bed granules with good flow properties and suitable aqueous redispersion. The chitosan coating of the nanocapsules improved granule redispersibility. The aim of the present study was to evaluate the influence of the amount of binder system (phenytoin-loaded nanocapsules) on growth behaviour, flow properties, and *in vitro* drug release of granules.

A suspension of phenytoin-loaded nanocapsules was prepared by solvent displacement. This suspension was sprayed (top-down system) onto the fluidized bed containing a mixture of maltodextrin and phenytoin (1:0.004 w/w) as substrate. A sample (1.5 g) was collected after spraying 50, 100, 150 and 200 mL of the nanosuspension for particle size measurements by laser diffraction and SEM analysis. The granules were also characterized by cohesion and caking tests on a texture analyser. The linear correlation (r = 0.9863) between the volume of nanocapsule suspension sprayed and the mean particle size indicated a granule growth index of 135%. SEM images showed no primary maltodextrin particles in granules after spraying 100 mL of the nanocapsule suspension. This finding was in agreement with the presence of well-defined solid bridges in the granule structure. In addition, the Surface Area Coverage % ($SAC_{guest\text{-}host}$) of the granules prepared with 200 mL of the binding system was 63.5%. This indicates the transition from guest-host to guest-guest contact between the nanocapsules, suggesting their arrangement in the solid bridges and confirming Raman images, in which the nanocapsules could be seen distributed on the granule surface. Regarding flow properties, granules showed a cohesive nature, although no powder segregation potential was observed in the texture analysis. Therefore, the volume of the nanocapsule suspension sprayed on the maltodextrin/phenytoin bed influences granule growth behaviour and, consequently, the final drug content of nanocapsules. In addition, nanocapsules were responsible for the controlled agglomeration of the particles and controlled drug release. Their promising use as a technological approach in granulation processes is highlighted.

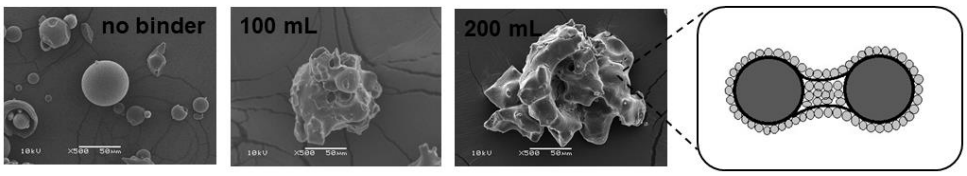

Figure 1: SEM images of the fluidized granules before and after the granulation process. This figure shows a model of the surface coating and solid bridges by/with nanocapsules.

[1] R.B. Friedrich, M.C. Fontana, M.O. Bastos, A.R. Pohlmann, S. S. Guterres, R.C.R. Beck. Drying Polymeric Drug-Loaded Nanocapsules: The Wet Granulation Process as a Promising Approach, Journal of Nanoscience and Nanotechnology, 10 (2010), 616–621.

35. DISCRETE-ELEMENT SIMULATION OF BREAKAGE INSIDE BALL MILLS

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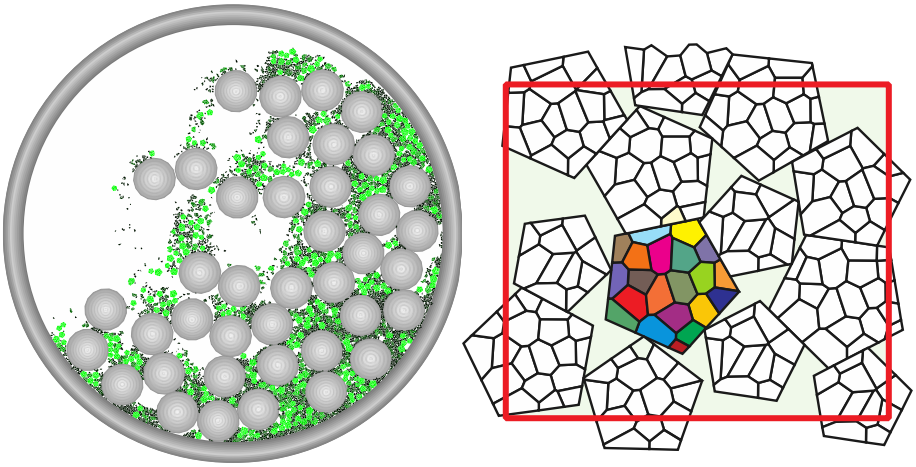
Ball mills are widely used in the industry for a large set of application as: grinding, breakage, mixing, among others. Applications in which the main objective is changing the particle size distribution of the material (i.e. particle breakage), depend on the mechanical events that the particles are subjected to. Mechanical properties in granular materials under dynamic conditions are difficult to measure experimentally. Simulation tools present limitations and challenges in these cases. However, by choosing the adequate model and the correct parameters, results provide insights into the interactions between powder, grinding balls and drum walls at the particle and contact scale. By means of 2D simulations using a DEM method known as Contact Dynamics and applying the bonded cell method (BCM) [1] for modelling breakable particles, simulations on the grinding of a powder inside a ball mill were performed. Samples with different grinding media size and quantity were tested in order to study the particle fragmentation modes that take place inside the system. Also, we determined the spatial distribution of the breakage events, and measured evolution of powder properties such as: damage degree, specific surface and particle size distribution.



(a) (b)

Figure 1. (a) Snapshot of a 2D DEM model of a ball mill. The powder is presented in green: the brightest colour is for the intact particles and the darkest for the completely damaged ones. Grinding media are considered as disks and presented in grey colour. (b) Snapshot of some particles at the initial state. Each colour represents a cell or potential fragment; the configuration is obtained applying a Voronoï tessellation [1].

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36. DEM-PBM COUPLING FOR MULTISCALE ANALYSIS OF TWO-COMPONENT HIGH-SHEAR WET GRANULATION PROCESSES

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The multiscale modelling implies simultaneous treatment of specific problem on different time and length scales. Application of this methodology in the area of solids process engineering allows simulating of industrial scale processes considering microscale characteristics of materials. In recent years, this technique has been widely applied for simulation of single component granulation processes [1, 2]. However, there are still numerous challenges, which are mostly related to the high computational effort on the microscale and the need to understand collision-scale behaviour of two-component systems which are widely applicable in numerous industries such as pharmaceuticals.

In this contribution, we propose a multiscale simulation framework with direct coupling of the discrete element method (DEM) and the population balance models (PBM). This system was applied for modelling of a two-component high-shear wet granulation process (Figure 1) consisting of an API and an excipient. In order to reduce the computational time, the DEM simulation system MUSEN was used. Due to highly efficient parallel CUDA-based computations and the simultaneous usage of CPU and GPU, this system can be effectively used on a personal computer. For the macroscale calculation of the granulation unit and interconnected apparatuses, the dynamic flowsheet simulation framework DYSSOL was applied. The data transfer between micro and macroscales was carried out in two directions. On the one hand, the results of the DEM calculations were used to predict kinetics of the PBM. On the other hand, the DEM model was regenerated during simulation according to the state of the macroscopic process. We compare the coupled PBM-DEM results to experimental findings to demonstrate the validity of the multi-scale scheme.

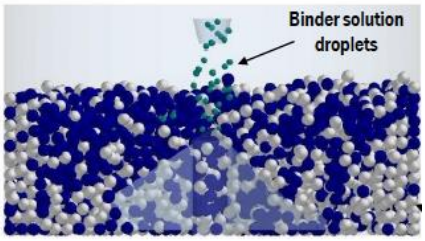

Figure 1. DEM simulation of high-shear wet granulator.

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[2] D. Barrasso, R. Ramachandran, Qualitative assessment of a multi-scale, compartmental PBM-DEM model of a continuous twin-screw wet granulation process. Journal of Pharmaceutical Innovation, 11 (2015) 231-249.

37. GROWTH AND TRANSFORMATION OF CARBONATES BY AEROBIC BIOMEDIATION

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Artificial methods to produce dolomite are mainly due to inorganic chemical reaction [1], and anoxic biomediated process [2]. These methods have been mostly used to solve “the dolomite problem” in geology. On the other hand, the formation of dolomite can be used as one of the bio-cement materials [3], because it is chemically and physically more stable than calcite. Therefore, it is required to investigate the process of dolomite formation. In this study, aerobic biomediation technique [3], which can produce large carbonate particles at low temperature, is examined using a digital microscope and SEM.

The biomediated precipitation of carbonate was examined using Ca2+ and Mg2+ and urea as biodegradable organic matter. Under the existence of Ca2+ and Mg2+, the precipitation mechanism of carbonates was quite different from the case that only Ca2+ was used. The mechanism was complicated in terms of chemical reaction, morphology, mineralogy, etc. To explain the process, the electric double layer theory and selective adsorption of Ca ions were considered. Morphologically, the process was divided into four stages. First stage is explained by growing of amorphous calcium carbonate (ACC), as similar to inorganic process [1], possibly amorphous calcite with a small amount of Mg. This is considered to be due to selective adsorption of Ca2+ onto microbes.

When Mg2+/Ca2+ ratio becomes high, the different effect of Mg2+appears, which can be identified as the transformation to calcium carbonate monohydrate and/or aragonite (stage 2). When Mg2+/Ca2+ ratio becomes very high, Mg2+seems to coat the aragonite crystals. Then, the aragonite changes to proto-dolomite (stage 3). It takes time to reach Stage 4, because the transformation from proto-dolomite to crystalline dolomite may need external factors, such as drying and/or high temperature.

[1] J. D. Rodriguez-Blanco, S. Shaw, L. G. Benning, A route for the direct crystallization of dolomite, American Mineralogist, 100 (2015) 1172–1181.

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[3] M. Fukue, S-I, Ono, Y. Sato, Cementation of sands due to microbiologically-induced carbonate, Soils and Foundations, 51 (1) (2011) 83-93.

38. EXTENDED APPLICATION OF A MECHANISTIC MODEL FOR INTERPRETING GRANULATION OF VARIOUS IRON ORE TYPES

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A mechanistic model for interpreting the influence of feed characteristics on granulation effectiveness was previously proposed by J.D. Litster *et al*. [1]. This model was manifested to be applicable to simplified iron ore mixtures at low granulation moisture contents. However, it hasn't been verified on a wider range of iron ore types and higher moisture contents yet. Moreover, a particular knowledge of the relationship between the granulation effectiveness of single ores and feed characteristics is expected to be useful for evaluation of new ore types.

In this work, the mechanistic model was applied to establish quantitative understanding of the effect of ore characteristics on granulation effectiveness of single ores. The granulation experiments of five iron ore types were conducted in a laboratory granulation drum using water as binder. A wide range of moisture contents were tested for each ore type. The results show that the granulation effectiveness varies markedly with ore type and moisture content. Feed size distribution and moisture content are dominant factors determining the granulation effectiveness of single ores. The model is applicable for some ore types except for those with excessive intermediate particles or high amounts of ultrafine particles, which is more likely to yield poorer permeability of granulated materials. Hence, we proposed an empirical criteria for determining the applicability of the model.

[1] J.D. Litster and A.G. Waters, Influence of the material properties of iron ore sinter feed on granulation effectiveness, *Powder Technology*, 55 (1988) 141-151.

39. MORPHOLOGY STUDIES OF DRIED SALT MICRO DROPLETS

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The drying behavior of solid containing water droplets has attracted significant scientific interest in the last years. The solids, which are colloidal particles or soluble salts, form characteristic deposit structures according to the conditions during the drying process. The drying of single droplets has been investigated from various viewpoints to gain insight on factors that have a significant impact on the structure formation. This study presents new approaches to investigate the structure of deposit resulting from drying of solid containing micro droplets.

The three-dimensional analysis of the dried droplets is measured with White-Light-Interferometry (WLI) and transformed into a two-dimensional shape using Monte-Carlo method, whereby the droplet geometry is reduced to an axis-symmetric height profile [1]. In addition to that, it is possible to convert the obtained three-dimensional data from the WLI measurement into a height density distribution and to describe the characterization of the deposition structures by means of standard deviation, variance and skewness. The dried deposits were also investigated using X-ray micro-computed tomography in order to learn how the micro- and macro porosities of the deposits are influenced by the process parameters during the drying process. It will be shown that drying conditions influence strongly the final structure, the so called “footprint” as well as the internal porosity. This dependency may contribute to better understanding of particle-forming processes, such as fluidized bed coating.

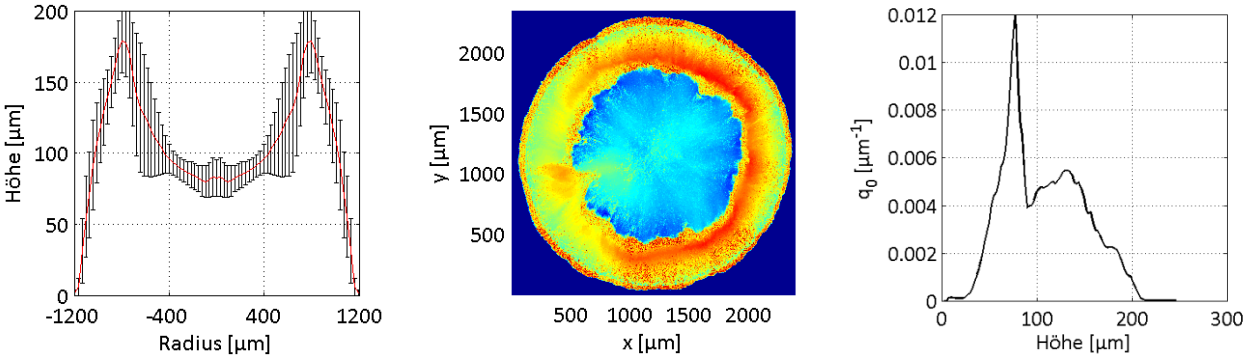

Figure 1. Three-dimensional analysis of the dried droplets using WLI. Left: mean height profile of a dried droplets with error bars showing the standard deviation, middle: topographic view of a single droplet, right: density distribution of the heights of the single droplet.

[1] Sondej, F., Peglow, M., Bück, A., Tsotsas, E. (2018) Experimental investigation of the morphology of salt deposits from drying sessile droplets by white-light interferometry. AIChE Journal 6 (6) (2018) 2002-2016.

40. MEASURING RIBBON STRENGTH AT A GERTEIS PACTOR DURING THE GRANULATION PROCESS

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Density is the most important parameter in solid dosage form development. During roller compaction, the in-line density is mostly driven by the applied force and the gap. Within a batch, the density and the ribbon strength are uniquely related. Due to batch-to-batch variation, the same density does not necessarily lead to the same strength. If for example the blending time for Vivapur 101 with 0.5 Magnesium Stearate is extended, equal tablet densities will result in lower tablet strength as shown in the figure below. Therefore, particle size distributions as well as recompactability behaviour of the granulates will be different. Hence, preferably the quality of granulates should be derived from ribbon strength measurements.

The GERTEIS PACTOR has been equipped with a special microphone inside the process area and an acceleration sensor to determine acoustic and vibration signals during the milling process. The signals show a good correlation with the ribbon strength even when changing parameters like roll speed, milling gap, screen size and materials. Especially, in the relevant range of tensile strength the signals are reproducible. All this makes the in-line measurement system for ribbon strength to a valuable PAT tool, which additionally enables a deeper insight in the dry granulation process.

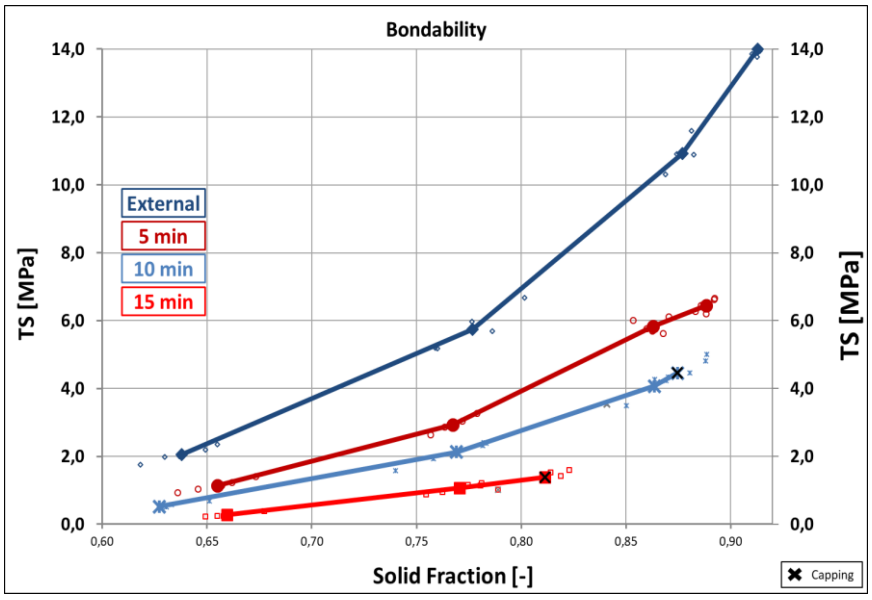

Figure 1. Bondability for different blending times, resulting in different tensile strength values at same solid fraction

41. MEASURING DEFORMATION BEHAVIOUR WITH ULTRASONIC DURING COMPACTION AT A STYL'ONE EVOLUTION

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Characterizing deformation behaviour of substances belongs to the key challenges in formulation development. There is no proven tooling to really analyse this. Often, the yield pressure is determined according to Heckel, but it does not provide information of elastic properties or pressure transmission to the die wall at all. As a new PAT, Kilian instrumented a pair of special punches with ultrasonic transceivers to send ultrasonic waves through the powder bed during tableting. By analysing longitudinal and transversal ultrasonic waves concerning speed and intensity, several compaction properties of powders can be determined.

The beginning of the decompression phase is a good indicator for the elastic recovery of substances. Also, the influence of tableting speed on the elastic behaviour can be derived easily. These are valuable information for the mechanical compatibility of materials. By calculating the Young's modulus of elasticity from the ratio of longitudinal and transversal ultrasonic speed a quantitative measurement of the elasticity during compression can be obtained.

Additionally, from longitudinal and transversal ultrasonic speed the Poisson's ratio, which is an indicator for pressure transfer to the die wall, can be calculated. Deformation properties of substances can be derived by plotting Poisson's ratio versus solid fraction. Plastically deforming materials appeared to have a linearly increasing Poisson number, whereas brittle fracture materials turned out to have one which is independent of the solid fraction (see figure below). Obviously, also a change in deformation behaviour upon an increase of solid fraction can be detected. Such deformation behaviour cannot be obtained easily from Heckel Plots.

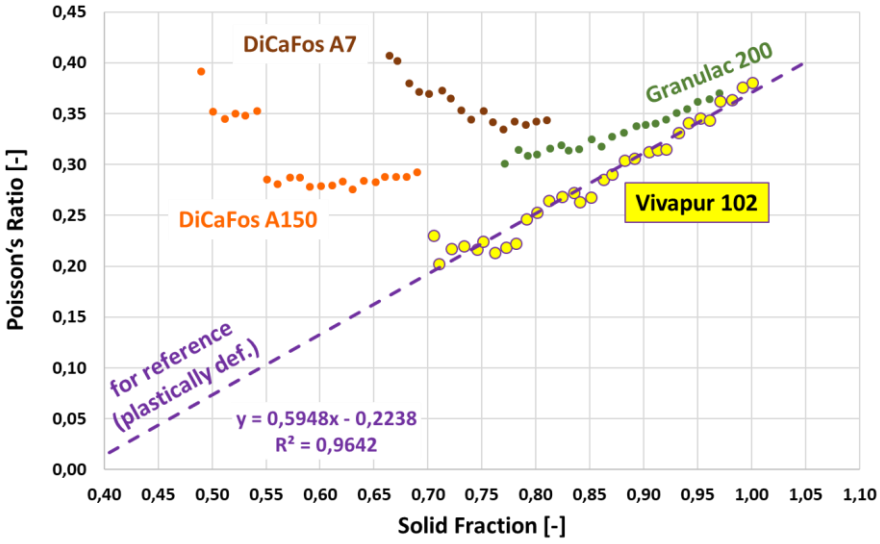

Figure 1. Poisson's ratio vs Solid Fraction for several substances showing different deformation behaviour

42. FINITE ELEMENT ANALYSIS: FEEDING POWDER FLOW IN ROLLER COMPACTION

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Roller compaction is a well-established continuous dry granulation process, where the powder is continuously compressed between two counter-rotating rollers and compacted into a ribbon followed by crushing into granules. The quality and homogeneity of the granules are determined by the uniformity of the ribbon properties across the ribbon width, such as porosity. This study evaluates the experimental results with three-dimensional finite-element analysis using arbitrary Lagrangian-Eulerian approach. A Drucker-Prager/cap constitutive model concept was used for the mechanical behaviour of the powder. The temperature profile and porosity across the ribbon width were measured to evaluate the homogeneity of the ribbon properties, which is compared with the results from a 3D finite element model. The finite element analysis agrees with experimental results and proves the concept of the significance to improve the feeding system to increase the uniform density distribution across the ribbon width.

43. STRATEGY FOR COATING OF AEROGELS IN A SPOUTED BED

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In this work a strategy for coating of microporous organic materials, such as aerogels, in a spouted bed is developed. Aerogels are open-pore structured and very light materials, which are applied in pharmaceutical and food products as carrier materials for active ingredients. In order to keep the 3D network and the active compound unaffected during storage and transport, the particles can be coated with thin polymeric films. Hence, coating prevents collapse of the porous network due to high capillary forces resulting from water penetration or high air humidity. Moreover, coating enhances mechanical stability and release properties, stabilizes the encapsulated drug, provides glossy surface, masks taste or reduces abrasion.

For the coating of aerogels two different types of materials are used: solutions and melts. Both of them can affect the porous structure of the particles during coating differently and require various process conditions. In case of using solutions, penetration of the pores due to the low-viscosity solvent can take place before its evaporation and thus, lead to collapse of the network. Additionally, evaporation of the solvent and consequently lower concentration of the coating material require longer processing times to get the same film thickness compared to melts. However, the temperature during spray coating with melts needs to be carefully chosen. The application of melts requires higher process temperatures, which can destroy the particles due to the thermal stress, but too low temperature causes too fast solidification and formation of solid bridges and agglomerates. Nevertheless, the influence of process parameters like viscosity, bed temperature, droplet size or spray rate on the quality of the aerogel particles and uniformity of the coating are investigated. Therefore, the coated particles are cross-sectioned using focused ion beam (Fig. 1) to evaluate the interface between particle and coating layer. Based on these investigations, the question, which kind of material at which process conditions is qualified for coating of aerogels to protect the porous network and form shell-core structure, is answered.

Additionally, coupled CFD (Computational Fluid Dynamics) - DEM (Discrete Element Method) simulations are performed to investigate the stability of the spouting process and optimize the coating parameters. These include determination of the residence time of the particles in the spray zone and its influence on coating layer thickness.

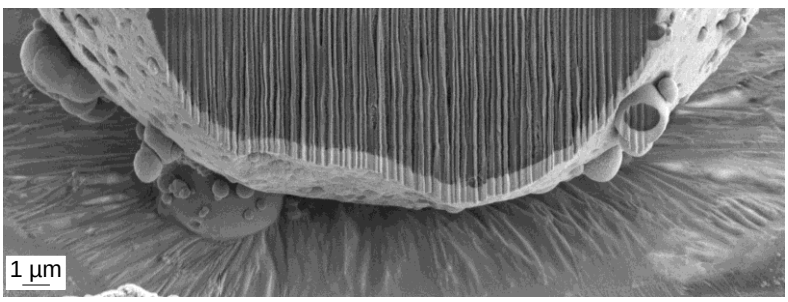

Figure 1. Cross-sectioned aerogel particle coated with a polymeric film.

44. MECHANISTIC CONSIDERATION OF MICRO-PROCESSES DURING COMPRESSION OF WELL-DEFINED MODEL POWDERS

Isabell Wünsch[1,2], Alexander Diener[1], Jan. H. Finke[1,2], Edgar John[3], Michael Juhnke[3] & Arno Kwade[1,2]

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The reliable prediction of structural and mechanical tablet properties based on material and process parameters is still not possible because of the insufficient in-depth understanding of the powder compaction process. This can be traced back to the complex material behaviour, the high number of influencing process parameters as well as on the complexity of the powder compaction process itself. The complexity arises from different and simultaneously acting micro-processes, such as particle rearrangement, elastic and plastic deformation and fragmentation of agglomerates/aggregates and primary particles. The differentiation between these micro-processes over the compaction process is difficult and in detail not possible until now. Additionally, the shares of the different micro-processes are dependent on the used materials and process parameters. The consideration of the compression behaviour of well-defined model materials with a spherical particle shape and defined deformation behaviour (ductile/brittle) is useful for the improvement of the process understanding and, thus, is the focus of this study.

Microcrystalline cellulose spheres (MCC) with a ductile deformation behaviour and glass beads with a brittle behaviour are selected as well-defined model materials. The compression behaviour of both materials and their binary mixtures is characterized using the compaction simulator Styl'One Evolution (Medel'Pharm, France), which is a single station tablet press equipped with force and displacement sensors. The extended in-die compression function [1] was applied to the in-die compression curves for the derivation of characteristic compression parameters. The deformation state of the single particles is characterized by scanning electron microscopy, particle size and shape analysis, and gas adsorption measurements. It is found, that the contact area between two MCC particles flattens with rising compression stress due to plastic deformation, while the amount of fines rises for glass beads because of particle breakage. The amount of plastic deformation/particle breakage decreases with decreasing initial particle size. This observation correlates well with the increasing compression modulus derived by the extended in-die compression function and can be explained by the larger resistance against deformation of finer particles. The deformation behaviour of binary mixtures of both materials with comparable particle size distributions depends on the contact probability of the different materials. The predominant mechanism changes from ductile below a glass concentration of 50 vol.-% to brittle above 50 vol.-%. Additionally, X-ray microtomography is used for in situ measurements of compression to gain reliable micro-process information at lower compression stresses. The generated data is used for the deduction of the acting micro-processes at different compression stress levels and for the mechanistic correlation of the derived characteristic compression parameters with the acting micro-processes and underlying material parameters.

[1] I. Krautstrunk, J.H. Finke, E. John, M. Juhnke, A. Kwade, A modified process function for the description of the powder compaction process, 8th International Granulation Workshop 2017, Sheffield.

45. STRATEGIES FOR OVERCOMING WINDOW FOULING DURING IN-LINE REAL-TIME MONITORING OF FLUID BED GRANULATION

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Fouling in Fluid Bed Granulation can significantly impact product quality, process reliability, efficiency and yield and impede real-time, in-line measurement of critical quality attributes using process analytical technology (PAT). This results in increased waste due to batch failure, greater burden on man-hours and higher production costs. The effect of fouling on moisture analysis was demonstrated using an NIR spectrophotometer fitted with contact and non-contact fibre optic probes. Two methods were employed to mitigate fouling to improve real-time in-line measurement: a process window wiper with a non-contact probe and a contact probe. Chemometric models were prepared by correlating Loss on drying measurements to spectral data with Quanta Model Developer, using Partial Least Squares Regression to analyse each of the setups. When fouling occurred with the standard non-contact method, the root-mean-square error of prediction (RMSEP) increased from 2.5% to 20%. Using a contact probe, the RMSEP fell to 1.5% but using a non-contact probe with wiper significantly improved the predictive accuracy, yielding an RMSEP of 0.7%, averaged across the duration of the process and across multiple batches. This demonstrates that fouling significantly impedes the ability of sensors to analyse processes, but that the effects can best be mitigated using a process window wiper. Furthermore, this indicates that the accuracy of real-time monitoring of fluid bed granulation using PAT can be greatly improved opening the potential for using NIR measurements in an automated control strategy.

46. PERFORMANCE COMPARISON OF DOME AND BASKET EXTRUSION GRANULATION

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A water dispersible granule (WG) formulation is a dry formulation containing active ingredients intended to be diluted and dispersed in water prior to application. If the co-formulants are correctly selected, WGs typically have good physical and chemical stability. In addition, storage and transportation of dry formulations, such as WGs, are inherently easier than liquid formulation types, and are less dusty than other dry formulations such as wettable powders (WP).

WG formulations can be made by several processing routes, with extrusion being the most common. Granules created by the extrusion process usually have good resistance to attrition and relatively high density compared to WP formulations. Dispersion time is a key performance test to evaluate WG formulations.

There are two common paste extrusion methods: basket and dome extrusion. Basket extrusion seems to be generally more forgiving as products designed to be dome extruded can normally be basket extruded, but not vice versa. In this work, premixes varying from primarily water insoluble components to primarily water soluble components are extruded using these two technologies. The granules are dried using a lab scale vibratory fluidized bed. The final products are compared in terms of various performance criteria: dispersion, density, suspensibility, and dry blending.

47. IMPLEMENTATION OF ROUNDING MECHANISMS IN DEM SIMULATION OF THE SPHERONIZATION PROCESS

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In the production of pharmaceutical pellets with a narrow size distribution and a high sphericity, a combined extrusion-spheronization process is commonly used. The rounding of the wet cylindrical extrudates in the spheronizer after the extrusion step is influenced by various overlapping mechanisms, in particular plastic deformation, breakage, attrition and coalescence. Due to the interdependency of those mechanisms as well as their dependency on the particle dynamics [1], there is no sufficient description of the pellet rounding in the spheronizer. In this study, simulations with the Discrete Element Method (DEM) are coupled with a Population Balance Model (PBM) to account for the rounding mechanisms.

For the description of the deformation behaviour of the pellets in the DEM a contact model for the wet pellets is needed, therefore a model was developed based on single particle compression and impact experiments with spheronized pellets. A multi-sphere approach [2] was used to approximate the pellet shapes in the DEM simulation. For an aspect ratio of 1.7 the possible shapes are exemplarily shown in Fig. 1. In order to realise the simulation of the whole process time, the coupled PBM operates on a larger time scale than the DEM. Therefore, the particle collisions are processed statistically and it is assumed that the collision characteristics do not change during the time span the PBM is allied. After the PBM was applied, the pellet shape is updated, if necessary. From these simulations detailed information about rounding processes in the spheronizer can be gathered.

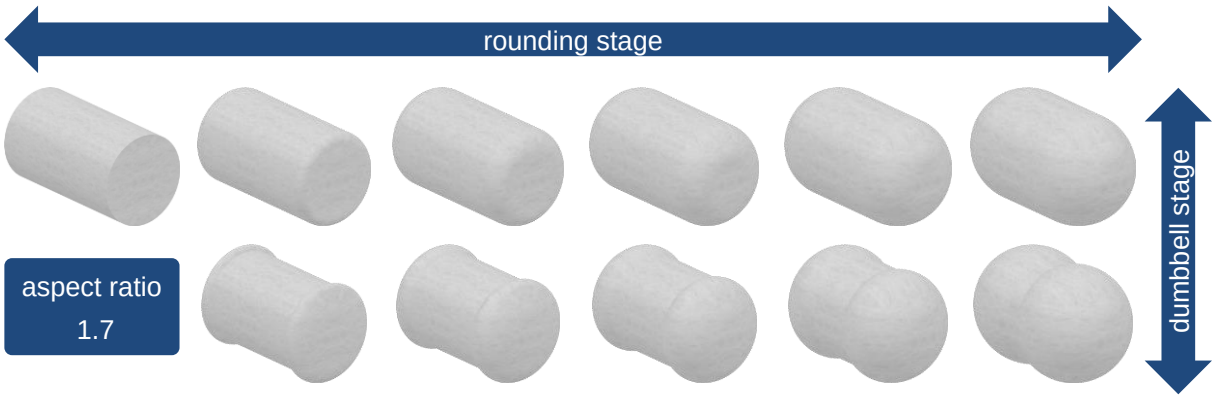

Figure 1. Exemplarily shapes used in the simulation for pellets with an aspect ratio of 1.7

[1] D. Weis, M. Niesing, M. Thommes, S. Antonyuk, DEM simulations of the mixing behavior in a spheronization process, Chemical Engineering Science, 192 (2018) 803-815.

[2] J.F. Favier, M.H. Abbaspour-Fard, M. Kremmer, A.O. Raji, Shape representation of axisymmetrical, non-spherical particles in discrete element simulation using multi-element model particles, Engineering Computations, 16 (1999) 467-480.

48. DEVELOPMENT OF A CONTACT MODEL FOR WET PARTICLES FOR THE DEM SIMULATION OF THE SPHERONIZATION PROCESS

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In the pharmaceutical industry, pellets with a narrow size distribution and a high sphericity are commonly produced using a combined extrusion-spheronization process [1]. After the extrusion step, the wet cylindrical extrudates are rounded in the spheronizer. The pellet rounding in the spheronizer is influenced by various overlapping mechanisms, in particular plastic deformation, breakage, attrition and coalescence. Due to the interdependency of those mechanisms as well as their dependency on the particle dynamics [2], there is no sufficient description of the pellet rounding so far. With simulations using the Discrete Element Method (DEM), detailed information on the particle dynamics can be obtained. In this study, a contact model for the wet pellets was developed to describe the deformation behaviour of the particles in the simulations.

In order to find a suitable description of the deformation behaviour, numerous single particle compression and impact experiments were performed with spheronized pellets. The force-displacement behaviour, obtained in the uniaxial compression tests, is described with a linear relation for loading and a non-linear relation for the unloading case (see Figure 1). Based on the uniaxial compression tests, the energy dissipation is modelled as a function of the loading energy. Moreover, in the developed model the cyclic loading of pellets is considered. Therefore the stiffnesses for loading and unloading as well as the energy dissipation are a function of the cycle number. The developed contact model was implemented in the DEM framework and simulations of the spheronization process were performed.

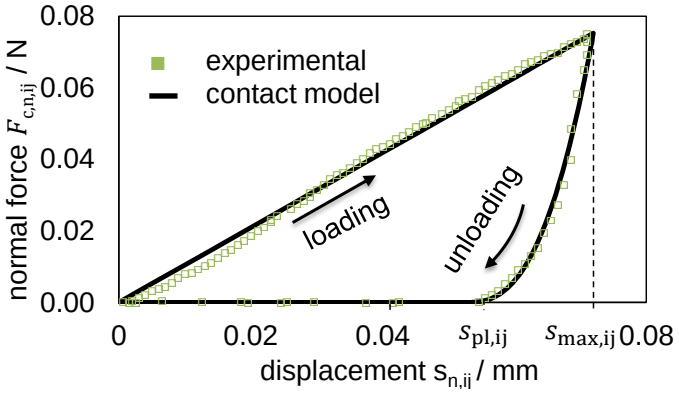

Figure 1. Characteristic force-displacement behaviour of the pellets obtained in uniaxial compression tests approximated with the developed model

[1] S. Muley, T. Nandgude, S. Poddar, Extrusion–spheronization a promising pelletization technique: In-depth review, Asian Journal of Pharmaceutical Sciences, 11 (2016) 684-699.

[2] D. Weis, M. Niesing, M. Thommes, S. Antonyuk, DEM simulations of the mixing behavior in a spheronization process, Chemical Engineering Science, 192 (2018) 803-815.

49. DYNAMIC BEHAVIOUR OF THE SPRAY GRANULATION IN CONTINUOUSLY OPERATED HORIZONTAL FLUIDISED BEDS

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In continuous spray granulation processes very often horizontally constructed fluidised beds with rectangular cross sections are used, which are divided by a variable number of plates (weirs) into several chambers of different functionalities. Commonly an external product processing, consisting of pneumatic conveying, screening, grinding of the oversize granules and recycling of grinded oversize and undersize granular material into the fluidised bed granulator is applied. The resulting internal and external networks of solids process unit operations as well as gas, liquid and solid flows lead to a complex and dynamic process behaviour.

This work focuses on the dynamic behaviour of spray granulation processes in horizontal fluidised beds that affect the process conditions, as well as the product properties. Studying the dynamic effects of this process, on the one hand a holistic view on the macroscopic process is considered to characterize the process behaviour with respect to the stability and time constants of the rate processes. On the other hand the process is divided into local compartments to analyse several sub-processes and their effects within the granulation individually, such as the spraying process within the spray zone and the solids residence time and transport through the multi-staged process chamber under different weir configurations.

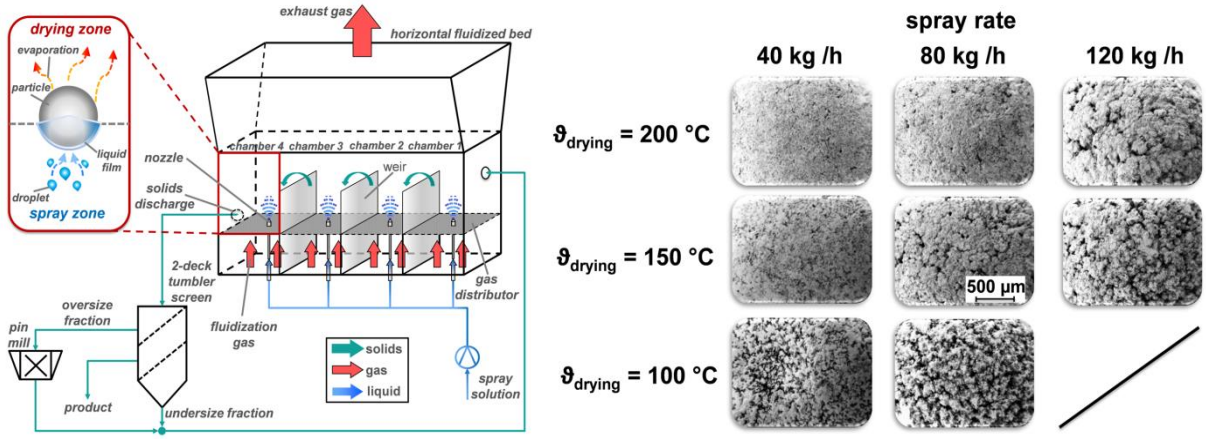

Figure 1. Simplified process flow diagram with schematic representation of the internal zone formation and external process chain (left); Influence of the process conditions onto the morphological structure (SEM pictures) of the product granules (right).

50. INFLUENCE OF CARRIER PARTICLE SOLUBILITY ON REDISPERSIBILITY OF NANOPARTICLE-LOADED GRANULES

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In recent years, the majority of newly assessed active pharmaceutical ingredients (APIs) are classified as poorly water soluble, resulting in compromised bioavailability. One possibility to overcome these challenges is to reduce the particle size of the API into the submicronic range, e.g. by wet media milling. However, for a final application nanosuspensions are usually converted into the solid state by suitable drying methods [1].

In this work, a fluidized bed granulation approach was applied for drying a naproxen nanosuspension. Thereby, the feasibility of applying a pure nanosuspension without additional excipients as a granulation liquid was investigated for carrier particles with varying properties. Furthermore, the effect of the amount of an additional polymer in the granulation fluid on the facilitation of an embedding of the nanoparticles in the dried state and, thereby, preserving the nanoparticulate state, was investigated for these carrier particles. It was found, that already a pure nanosuspension could be effectively utilized as a granulation liquid in a fluidized bed granulation process. However, the quality of obtained granules regarding nanoparticulate redispersibility was highly dependent on properties of the applied carrier particles. Dependent on their solubility, different degrees of embedding of the nanoparticles into the surface of the carrier particles, due to surface solution, could be observed, which qualitatively correlates with outcomes of redispersibility studies. Furthermore, it was shown that the concentration of additional polymer in the granulation fluid to yield granules being completely redispersible to the originally applied nanosuspension inversely correlates with the solubility of the applied carrier particles.

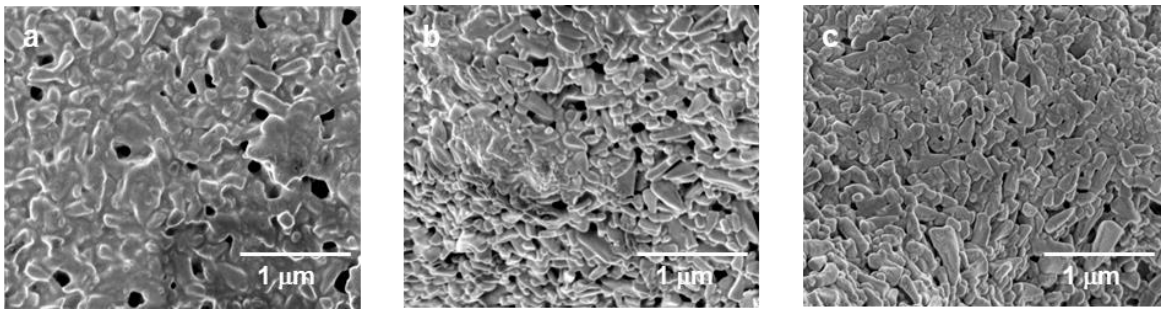

Figure 1. SEM images of the surface of nanoparticle-loaded granules produced by application of a pure nanosuspension (without additional polymeric binders) to carrier particles consisting of a) mannitol, b) monohydrous lactose, and c) microcrystalline cellulose

[1] B. Van Eerdenbrugh, G. Van den Mooter, P. Augustijns, Top-down production of nanocrystals: Nanosuspension stabilization, miniaturization and transformation into solid products, International Journal of Pharmaceutics, 364 (2008) 64-75

51. IMPROVEMENT OF TABLETABILITY VIA TWIN-SCREW MELT GRANULATION: FOCUS ON BINDER DISTRIBUTION

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The objective of the study was to investigate the influence of binder distribution on the tabletability of granules produced through twin-screw melt granulation. Dicalcium phosphate anhydrous as a model substance was melt granulated in a twin-screw extruder, using two different particle sizes of poloxamer in three different concentrations (5, 10, 15% w/w) as binding material. Compaction performance of the granules and the respective physical mixtures (PM) of the substances was evaluated. Binder distribution could be parameterized via image-analysis of the tablet surface using scanning electron microscopic energy-dispersive X-ray analysis (SEM/EDX).

Melt granulation facilitated a homogenous distribution of the plastically deforming binder throughout the brittle model substance. Exceeding a binder concentration of 10 % the homogeneous distribution resulted in a pronounced increase in tabletability and compressibility (data not shown).

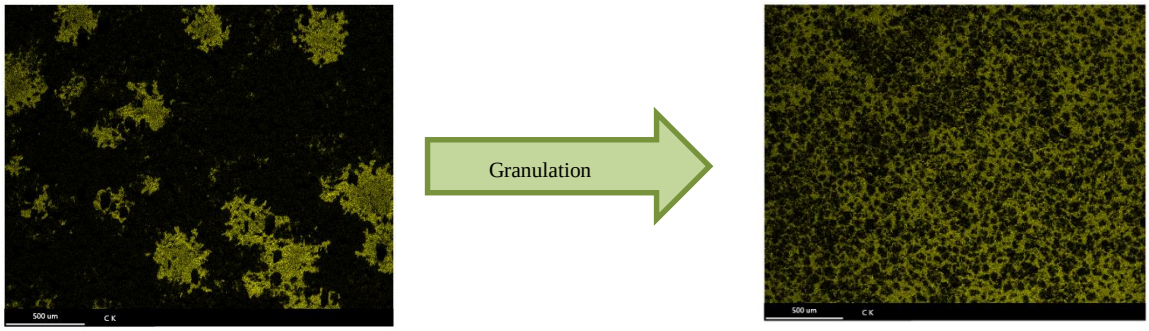

Figure 1. Tablet surface SEM/EDX maps of PM and granules: DI-CAFOS® A60 & Kolliphor® P407 15% w/w

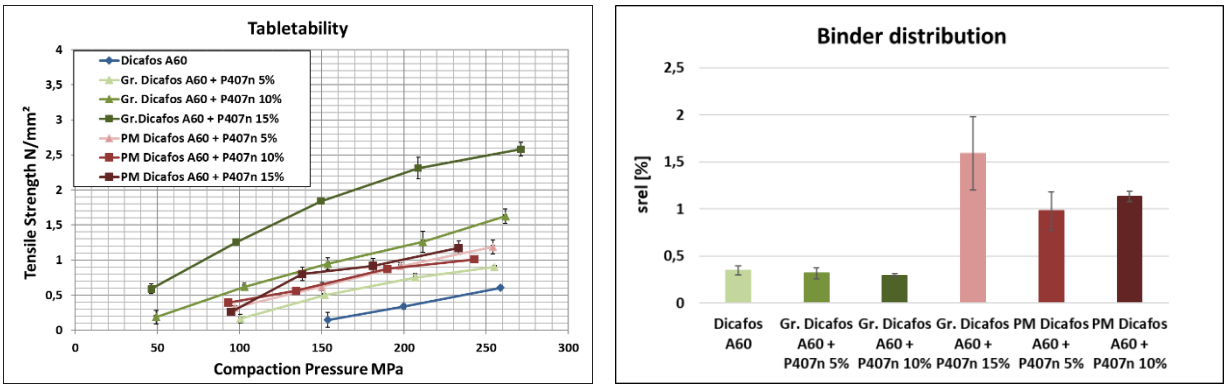

Figure 2. Tabletability of PM and granules: DI-CAFOS® A60 & Kolliphor® P407 (left), variance of binder distribution using image analysis (right)

52. FABRICATION OF HIGHLY-FILLED COMPOSITES USING SPOUTED BED SPRAY COATING

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Natural composite materials as bones, teeth and nacre show very good mechanical properties due to their high filling degrees on hard constituent. Furthermore the strong connection between the particles of the hard constituent and the polymer and their hierarchical structure contribute to those properties. To mimick the structure of the bio-composites a spouted bed spray granulation process was used to fabricate highly filled composite materials from various particles and polymers.

Spouted beds are used for many applications in solids process engineering as drying, mixing, coating and granulation. For the fabrication of composite materials spouted bed was used because very fine particles can be processed. The composites are fabricated by coating the fine particles with a polymer solution and further granulation of the bulk material. Besides fine particles of ceramics, copper and iron oxides, prestructured particle-polymer granules can be further processed to archive a higher level of hierarchy by granulation. For the process two scales of spouted beds are used. The process chambers are either conical or prismatic with a high conical-cylindrical relaxation zone. The injection of the polymeric binder was operated with a bottom-spay two-fluid nozzle, which contribute to a uniform coating of the particles. The smaller scale of the spouted bed allows working with smaller amounts of particles. Furthermore, the downsizing enables the processing under the fume hood and by that working with more volatile and toxic solvents e.g. for high performance polymers. After the coating and granulation mechanical properties of the composites are determined in bending tests.

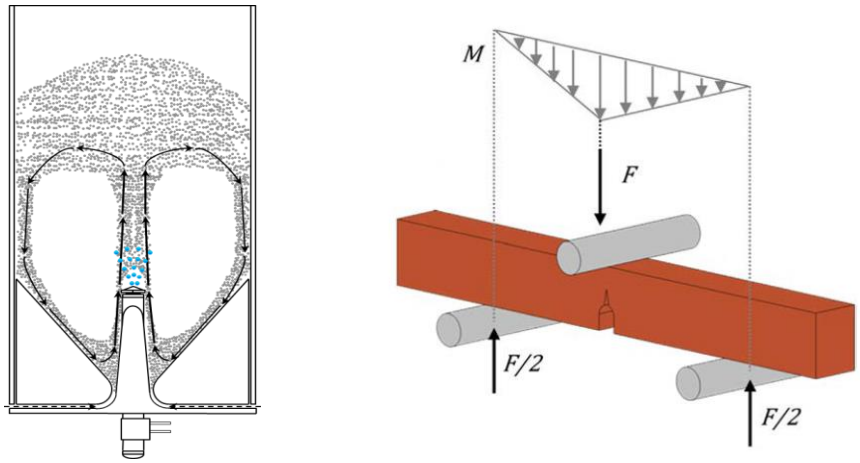

Figure 1. Particle movement in the process chamber of a spouted bed (left) and three-point bending-test for determination of mechanical properties (right).

53. AN INTEGRATED RATE PROCESSES MODEL FOR HIGH SHEAR WET GRANULATION AND ITS APPLICATION FOR SCALE-UP

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High shear wet granulation (HSWG) operation consists of several rate processes influenced by raw material properties, processing conditions and equipment design, that control the granule attributes. In literature, these rate processes have been modelled using different dimensionless numbers (power number correlation [1], nucleation regime map and growth regime map [2]). Each of these dimensionless numbers represent a particular rate process or granule quality attribute. Since these rate processes occur simultaneously, it is necessary to solve these dimensionless numbers together. This will lead to a robust scale-up.

An integrated rate process model of the HSWG operation has been developed by combining the correlations and relationships among all the relevant geometric, quality and operational parameters affecting the granule properties. The process model has been solved within a multi-objective optimization framework for designing experiments and computing the design space at the commercial scale that will produce granulation for manufacturing tablets with acceptable compaction properties. The figure below presents the variation of granule porosity at the commercial scale as a function of Froude number and liquid/solid ratio. The tablet tensile stress calculated from the predicted porosity shows good agreement with the measured data.

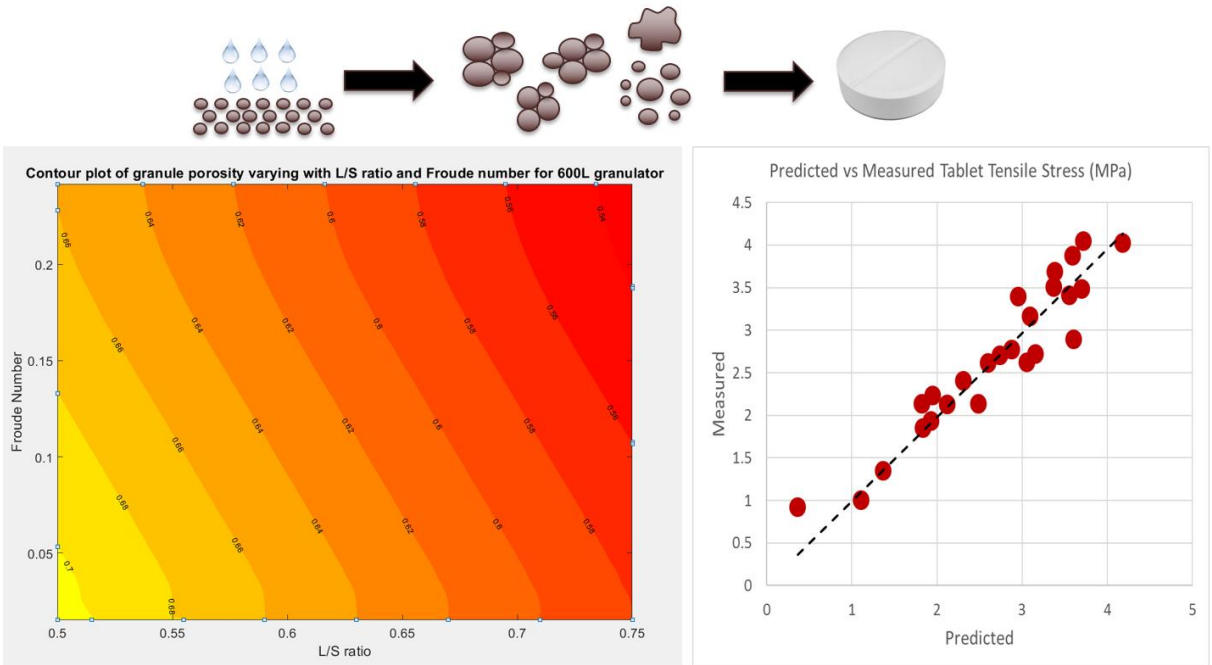

Figure 1. Design space at commercial scale

[1] A. Faure, I.M. Grimsey, R.C. Rowe, P. York, M.J. Cliff, Applicability of a scale-up methodology for wet granulation processes in Collette Gral high shear mixer-granulators, European Journal of Pharmaceutical Sciences, 8 (1999) 85-93.

[2] J.D. Litster, Scaleup of wet granulation processes: science not art, Powder Technology, 130 (2003) 35-40.

54. SCALING FROM COMPACTION SIMULATOR TO PRODUCTION ROTARY PRESSES - INTERPLAY OF MATERIAL PROPERTIES

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Tablets are the most frequently produced and applied dosage form. Nonetheless, their production process is not mechanistically understood, yet. Accordingly, formulation and process development of tablet production mostly rely on empirical trials and the practical knowledge of individuals. Additionally, results at lab scale are often not directly transferrable to production scale due to different filling regimes, compaction profiles, and specific velocities. To overcome these hurdles and to enable formulation and process development at small scale with a low consumption of material, compaction simulators were engineered. They try to circumvent challenges of different construction approaches and they are feasible to more flexibly address formulation and process issues than common tablet presses. The question remains, with which precision compaction simulation can capture the effetcs of diversity of process parameters and material properties in tableting as well as specific challenges of different sub-processes (feeding, filling, compaction profile, ejection).

In this study, compaction simulation is challenged, systematically evaluating the transferability of product properties (e.g. tensile strength, porosity) from a compaction simulator to different scales of rotary presses for common pharmaceutical ingredients. Crucial process and machine parameters are identified and elucidated. The precision of pressure-time profile resemblance by the compaction simulator was only found essential for visco-plastic materials such as starch. A special focus was set to the behaviour of multi-component blends of filler/filler as well as filler/lubricant. In this context, the necessity to precisely determine the effect of the feeding/filling system was emphasized. For material blends containing fillers only, a very good comparability of the product properties over process parameters was found. For lubricated powders of ductile materials, a drastic difference between compaction simulator and production rotary press was found. Hence, the applicability of the dimensionless Shear Number, introduced by Narang et al. [1], was investigated for such scaling purposes. A thorough investigation in the differences of filling systems made a modification of the Shear Number formula necessary to consider the functional principles of the respective feeder. With this modified formula, settings of rotary press feeders can be calculated to respective rotational frequencies of compaction simulator feeders (and vice versa) and, by that, practically achieve equal product properties in both processes. Accordingly, a scaling principle for direct transfer from compaction simulator to production rotary presses was derived, considering the crucial effect powder stressing during feeding.

[1] A.S. Narang, V.M. Rao, H. Guo,J. Lu, D.S. Desai, Effect of force feeder on tablet strength during compression, Int. J. Pharm. 401 (2010) 7-15.

55. AGGLOMERATION OF (NICKEL/MANGANESE/COBALT) HYDROXIDE IN TAYLOR VORTEX FLOW

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(Ni/Mn/Co) oxide is most promising cathodic material of battery for high electric capacity and performance. The electric capacity of cathode is not only determined by the composition but also the morphology of (Ni/Mn/Co) oxide particles. That is, the cathode of battery is capable of the higher electric charge/discharge, as the (Ni/Mn/Co) oxide is more packed in a fixed space of battery. So, the spherical shape is favored for high packing density of (Ni/Mn/Co) oxide in cathode. (Ni/Mn/Co) oxide is synthesized via thermal decomposition of (Ni/Mn/Co) hydroxide in solid state, which is precipitated by the reaction of (Ni/Mn/Co) sulfate and NaOH. Thus, the morphology of (Ni/Mn/Co) hydroxide in the precipitation is highly critical in predetermination of the electric capacity of cathode.

In previous works, the agglomerates of (Ni/Mn/Co) hydroxide were obtained by the reaction precipitation in mixing tank crystallizer, in which a fluid motion of turbulent eddy flow was generated by the impeller. So, it took over 12 hrs to obtain spherical agglomerates of (Ni/Mn/Co) hydroxide. Meanwhile, in the present work, the periodic fluid motion of Taylor vortex flow was applied in continuous mode to achieve spherical agglomerate of (Ni/Mn/Co) hydroxide. Due to uniform and effective fluid shear, Taylor vortex flow was much more effective for spherical agglomeration, resulting in a high tap density of 2.10 g/cm^3 of (Ni/Mn/Co) hydroxide. As increasing the Taylor vortex velocity, the agglomerate size was reduced and tap density was enhanced. Also, the agglomerate size and tap density depended on the wave length of Taylor vortex. These experimental results were well correlated with average shear rate of fluid [1].

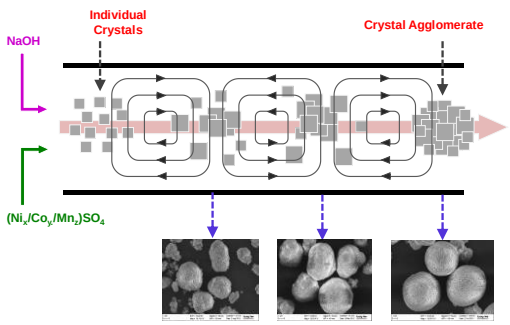

Figure 1. Agglomeration in Taylor vortex

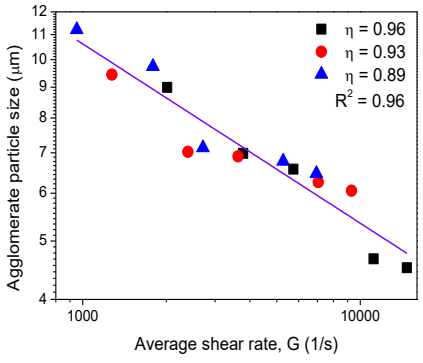

Figure 2. Correlation of agglomerate size to shear

[1] Q.-P. Mayra, W.-S. Kim, Agglomeration of Ni-rich hydroxide in reaction crystallization: Effect of Taylor vortex and intensity, Cryst. Growth. Des., 15 (2015) 1726-1736.

56. ESTIMATION ON THE CAPILLARY FORCE OF AN ASYMMETRIC LIQUID BRIDGE ADHERED TO TWO PARTICLES WITH NONCIRCULAR CONTACT LINE

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Estimation of interaction between particles with a binder liquid is important in controlling kinetics of agglomeration and handling of granular materials. The tensile strength of a powder bed depends on the static and dynamic capillary force of liquid bridges, which result in liquid distribution and liquid transfer within the interstices of particles. The normal capillary force of a pendular liquid bridge adhered to two particles has been numerically and experimentally investigated by Fisher, toroidal model and the exact solution of Yung-Laplace equation. However, the tangential capillary force has been not substantially evaluated due to the torsion of a liquid bridge by shear stress.

This work is aimed to numerically and experimentally estimate the tangential capillary force of a binding liquid adhered to two spheres. The figure shows the asymmetric liquid configuration with non-circular contact line. The normal and tangential tensile strength is measured by surface tensiometer and comparatively investigated by the numerical solution of Young-Laplace equation.

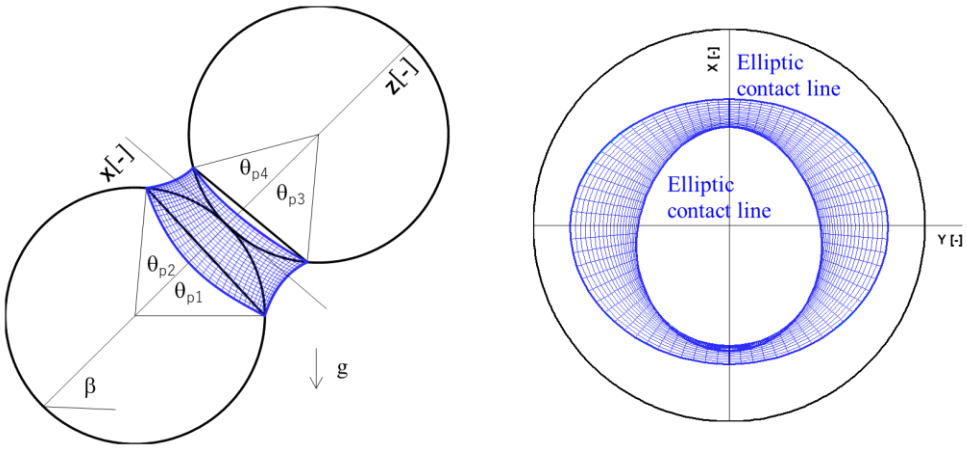

Figure 1. Asymmetric pendular liquid profile with non-circular contact lines.

57. EXAMINATION OF THE PHYSICAL & PERFORMANCE EFFECTS OF 2 DIFFERENT CONTROL MODELS ON SCALE-UP OF AN ENTERIC WURSTER COATING PROCESS

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Enteric coating is a common subsequent step to granulation / pelletisation in drug production, allowing formulators to create medications with release profiles that aid in improving efficacy, patient safety and compliance with reduced dosage frequency. These enteric coatings are typically polymer-based [1] and operate by creating a diffusion barrier around a drug-loaded particle which is often then encapsulated or compressed.[2] Unfortunately, as with many agglomerative and coating processes problems are very often encountered during the development stage when scaling-up process parameters developed at lab-scale.[3]

In this work a process for coating sugar spheres with propranolol, and then with Opadry EC to control release rate was benchmarked at 1.65kg lab-scale batch size (Glatt GPCG2) by means of assay, dissolution and offline particle size measurement as well as inline measurement of coating thickness change during processing using Eyecon$_2$ (Innopharma technology). This process was then scaled up to the 41kg batch size (Glatt GPCG 30 Wuster) where two different control regimes were applied to the enteric coating phase over the course of six batches. These two control regimes, one coating to the same weight-gain as at small scale, with the other coating until the same film thickness as at small-scale was achieved, were found to present significantly different results in terms of quantity of coating solution required and product performance (dissolution profile) of the final material. These results have the potential to influence design considerations in process development, scale up and control strategy and may open up an opportunity to more finely control product performance in a Wurster coating process.

[1] Peter J. Tarcha, Polymers for Controlled Drug Delivery, 1st ed., CRC Press, 1990.

[2] Hong Wen, Kinam Park, Oral Controlled Release Formulation Design and Drug Delivery: Theory to Practice, 1st ed., John Wiley & Sons, 2011.

[3] Michael Aulton, Graham Cole, John Hogan, Pharmaceutical Coating Technology, illustrated ed., Taylor & Francis, 1995.

58. INVESTIGATION OF THE MIXING CAPACITY OF A ROTARY TABLET PRESS FEED FRAME

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In tablet manufacturing product quality requirements are particular challenge as permitted quality deviations, for example deviations in content uniformity, are defined by legally binding guidelines (e.g. Ph. Eur.). Therefore, mixing operations are integrated into the process sequence to ensure an accurate mixing and powder distribution. Individual components of different apparatuses, such as a feed frame of a rotary tablet press, offer a certain mixing capacity. Cumulative residence time distribution (RTD) can be used as a first indicator for the mixing capacity of the system [1]. The aim of this study was the investigation of feed frame ability to blend powder before direct compression. Additional, the feasibility to compensate powder flow fluctuations above the feed frame should be examined.

Powder RTD in a rotary tablet press feed frame is measured while process parameters, for example paddle shape, are varied (Fig. 1). Deviations in mean residence times $\bar{t}$ and RTD spans can be measured: When using the rectangular paddles a longer mean residence time ($\bar{t}$ = 483 s) and a broader RTD (span = 2.4 s) is detected than applying round feed frame paddles ($\bar{t}$ = 446 s, span = 2.1 s). Generally, a wide RTD indicates a higher mixing efficiency due to a more powerful backmixing.

In addition to the actual functions, the feed frame of a rotary tablet press offer a certain mixing capacity. Using this would lead to a reduction of necessary upstream mixing steps and to a simplification of the process. A wide RTD could act as a first indicator for the opportunity to blend powder in the feed frame. Nevertheless, an experimental validation and a test for robustness are crucial to achieve a final conclusion whether a rotary tablet press feed frame can replace mixing steps.

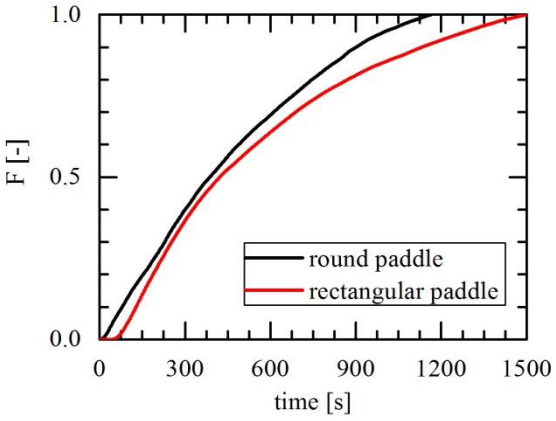

Figure 1. Cumulative RTD function F for two different paddle shapes.

[1] W. Engisch, F. Muzzio, Using Residence Time Distributions (RTDs) to Address the Traceability of Raw Materials in Continuous Pharmaceutical Manufacturing, Journal of Pharmaceutical Innovation, 11 (2016) 64–81.

59. ESTIMATION OF NIP ANGLE BY ROLL COMPACTION SIMULATION

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On a roll compactor (RC), the space between the rolls is divided into a slip, a compaction and a release zone. The angle between the beginning and the end of the compaction zone is called nip angle [1]. This angle is an important parameter for the process understanding. There are several approaches to determine the nip angle but they are instrumentally complex and not very feasible in practice. The aim of this study was to use a uniaxial compaction simulator (Styl'One Evolution, Medelpharm) for the nip angle determination.

RC of dibasic calcium phosphate (DCPA; DiCaFos A150, Budenheim), microcrystalline cellulose (MCC; Vivapur 102, JRS) and anhydrous lactose (Tablettose 80, Meggle) was mimicked on the Styl'One. Compacts (called ribblets) were produced at various gap widths (GWs) (2-4 mm) and specific compaction forces (SCFs) (5-15 kN/cm) with a constant roll speed of 2 rpm. The nip angle α can be calculated by the following equation:

$$\alpha = arccos\left(1 - \frac{(T_0 - T_1)}{D}\right)$$

T_0 is the powder bed thickness at zero pressure which corresponds to the angular position at the beginning of the compaction zone on the mimicked RC (Mini-Pactor, Gerteis). T_1 is the minimal distance between upper and lower punch during the compression which represents the GW. D is the roll diameter of the RC.

Both, GW and SCF, influence the nip angle. The coefficient plot (Fig.1 b) illustrates that an increase in GW and SCF leads to an increasing nip angle. The plastic material properties of MCC result in higher nip angles whereas the more brittle materials lactose and DCPA show smaller nip angles at the same SCF (Fig.1a, b). Our findings confirm values known from literature but so far, the nip angle calculation was not proven on a real RC.

This method is a promising simple approach to estimate the nip angle of a material. The impact of adding lubricants or APIs to the formulation and the influence of additional process parameters like the roll speed should be investigated.

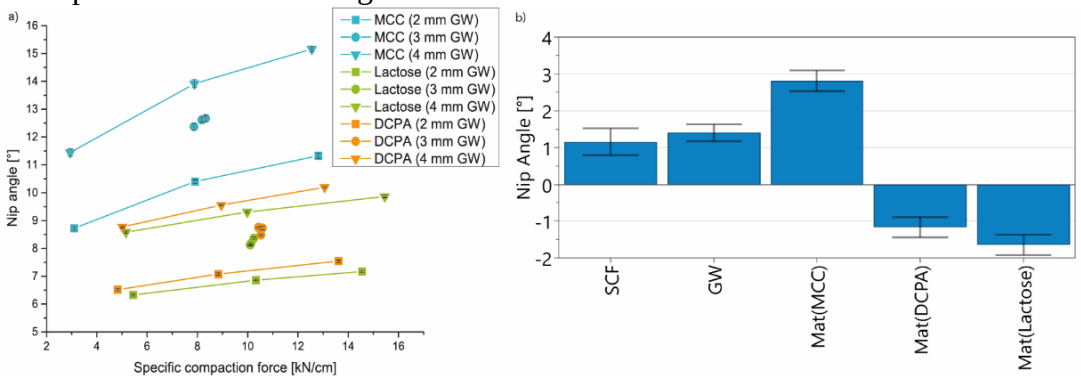

Figure 1. **a)** Nip angle of MCC, DCPA and lactose as a function of SCF (n ≥ 20; mean ± SD)
b) Coefficient plot

[1] J.R. Johanson, A Rolling Theory for Granular Solids, J. Appl. Mech., 32 (1965) 842-848.

60. DRAG RESISTANCE OF POROUS AGGLOMERATES IN FLUIDIZED BED GRANULATION

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Agglomeration is sticking of solid particles due to inherent interparticle forces (Van der Waals force, liquid bridge forces …) to form larger granules, leading to a growth of particle size over time. Agglomeration of bed materials is an important phenomenon in several applications that use fluidized bed technologies such as granulation, compacting, drying, combustion and gasification, etc. Agglomerates complicate the flow structure, thus influence the hydrodynamics as well as mass and heat transfer in fluidized beds. In fluidization, drag force is one of the dominant particle-fluid interactions to control particle movements, circulation and concentration distribution. Therefore, understanding and predicting the effect of agglomerates on the hydrodynamics (mainly gas-solid drag force) is crucial for the design and control of the desired process performance. Unfortunately, currently available drag correlations that are applied in modelling of fluidization do not truly take into account the agglomeration phenomenon [1].

Computationally, direct numerical simulations (DNS) is proven effective to study in detail the gas-solid interactions in multiphase flows. The hydrodynamic forces acting on the solid particles are directly computed in DNS from the fluid flow via enforcing a no-slip boundary condition at particle surface. DNS have been extensively used to develop drag correlations for suspensions of spherical particles in dilute and dense gas-solid flows for a wide range of Reynolds numbers and solid volume fractions. However, it is well understood that formation of agglomerates (similar to particle clusters) significantly reduces the drag force comparing to single particles. Thus, standard drag laws that are developed for spherical particles may overestimate the drag forces in the fluidized bed system with agglomeration phenomenon. Therefore, quantification of the mechanisms underlying particle agglomeration and their effect on the drag force using a first-principle based numerical model is crucial.

This work provides a detailed understanding and quantification of drag resistance of porous agglomerates in fluidized bed granulation using DNS. Agglomerates with different morphology (shape, size, porosity) are studied at different flow conditions (Reynolds numbers upto 200). By comparing all the simulation results to the existing drag correlations for non-spherical particles, a new drag correlation is formulated. This new correlation is a correction to the Schiller-Naumann [2] correlation for spheres but includes the dependency on the sphericity, convexity and normalized density of the agglomerates. The improved drag correlation can be used to improve the accuracy of prediction of CFD-DEM and TFM models for fluidized beds with agglomeration phenomenon.

[1] E. Loth, Drag of non-spherical solid particles of regular and irregular shape, Powder Technology, 182 (2008) 342-353.

[2] L. Schiller, Über die grundlegenden Berechnungen bei der Schwerkraftaufbereitung, Z. Vereines Deutscher Inge. 77 (1933) 318-321.

61. NUMERICAL SIMULATION OF PARTICLES MIXING EFFECT BETWEEN HIGH SPEED STIRRING MIXER AND CYLINDER MIXER

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The mixing effect of traditional cylinder mixer is poor under high load, and the size of quasi-particle is not uniform. In order to improve the current situation of poor mixing effect, this article respectively simulates the mixing behavior of sintering raw materials through high speed stirring mixer and cylinder mixer machines. Firstly, the difference of mixing effect between high speed mixer and traditional cylinder mixer is compared. Then the effect of rotating speed, number of stirring knives and other parameters on mixing effect are also researched. A comprehensive comparative analysis is conducted about the movement behavior of the particles and the mixing effect during the mixing process. Finally, through the simulation results, it can know that the mixing of high speed mixer is obviously better than cylinder mixer, no matter from the analysis of particle movement behavior or mixing effect.

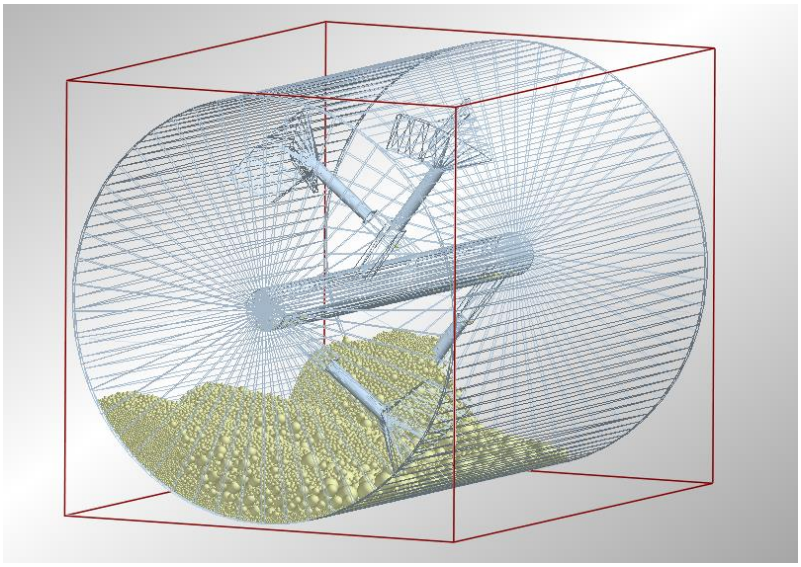

Figure 1. Dry particle flow in a high speed mixer

62. COMPACTION BEHAVIOUR ANALYSIS OF GRANULATED MATERIALS USING COOPER-EATON EQUATION

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Pharmaceutical powders are often dry granulated/roll compacted prior to die compaction in order to improve granules flowability. However, the major limitation of the process is the 'loss of tabletability' leading to a reduction in the tensile strength of tablets compared to direct compression of raw powders. This phenomenon had been researched extensively in the last few decades and is still considered to be a challenge.

The aim of the present work was to study the die-compaction behavior of granules obtained from microcrystalline cellulose (MCC 101) and Mannitol by dry granulation/roll compaction and to compare the behavior of granules with those of raw materials. The effect of roll force on the granules behavior during die-compaction was also investigated. MCC 101 and Mannitol were roll compacted at two different roll compaction forces to produce ribbons which were milled in to granules. The fractional volume compaction by particle rearrangement (filling of large pores) and by plastic deformation or fragmentation (filling of small pores) was analysed by Cooper-Eaton equation [1]. The prediction of granule strength from bulk compaction using the Adams model [2] was also discussed.

It was found for both materials, dry granulation/roll compaction improved the particle rearrangement during die compaction and the higher is the roll force, better is the rearrangement. For ductile material MCC, as the roll compaction force increases, the plastic deformation of granules is reduced due to the increased strength of granules. However, estimation of granule strength using the Adams model did not show agreement as it was expected. In contrast to MCC, brittle material mannitol did not show any significant difference during fragmentation neither due to granulation nor due to the increase of the roll force. Based on this investigation, it was demonstrated the ability of Cooper-Eaton model to represent the behaviour of both MCC and mannitol materials that develop different densification mechanisms during die compaction. This analysis needs to be extended to other materials to be confirmed.

[1] A.R. Cooper and L.E. Eaton, Compaction Behaviour of Several Ceramic Powders, Journal of the American Ceramic Society 45 (3) (1962) 97–101.

[2] M.J. Adams, M.A. Mullier, J.P.K. Seville, Agglomerate strength measurement using a uniaxial confined compression test, Powder Technology. 78 (1994) 5–13.

63. ROLLING PROCESS MODELLING & RELATED CHALLENGES

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Roll compaction process (RCP) is commonly used in particulate solids industries including pharmaceutical and mineral. In the pharmaceutical industry, RCP is employed as dry granulation method, well suited for active pharmaceutical ingredients to improve their flowability by increasing particle size and bulk density. In the mineral industry for cement, the main concern is to reduce the particle size and the specific surface with the objective to increase the reactivity of particulate solids. Using a roll press, the process operates as follows: the particulate solid is fed to the compaction zone either by gravitational feeding or by a screw feeder, then, drawn between two counter-rotating rolls in the stressing zone where the particle material undergoes fragmentation and/or consolidation.

In RCP two parts are combined to work in a coordinated manner, the feeding and the compacting systems. However the feeding is considered as the dominant part in the process that controls the throughput of roll press [1] and the ribbon homogeneity [2]. Moreover, because of the difficulty of ensuring a continuous and uniform flow of material, roll press is designed with a floating roll to adjust the gap to the variation of the incoming material flow. Taking into account these specifications in the modelling of RCP is still a challenge. The objective of this work is to present recent progress in modelling of RCP toward to better respect the functioning of the roll press, in particular:

(i) Modelling the flow of the material in the feeding system and the compaction between the rolls, recently developed in [3],

(ii) Attempting to take into account the fluctuation of the gap using a new modelling approach.

Predicted results are discussed based on the state of the art of knowledge on RCP and demonstrate the potential of modelling of RCP by providing important insight.

[1] P. Guigon, O. Simon, Roll press—influence of force feed systems on compaction, Powder Technology 130 (2003) 41–48.

[2] A.M. Miguelez-Moran, C.-Y. Wu, H. Dong, J.P.K. Seviller, Characterisation of density distributions in roller compacted ribbons using micro-indentation and X- ray micro-computed tomography, European Journal of Pharmaceutics and Biopharmaceutics 72 (2009) 173–182.

[3] A. Mazor, L. Orefice, A. Michrafy, A. De Ryck, J. G. Khinast, A combined DEM & FEM approach for modelling roll compaction process, Powder Technology 337 (2018) 3-16

64. MECHANISTIC MODELING OF SPHERICAL AGGLOMERATION PROCESS FOR PHARMACEUTICAL MANUFACTURING

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Spherical agglomeration process is a particle size enlargement technique which has recently been successfully applied in pharmaceutical production to improve the key properties of drugs such as flowability, compressibility, packability, and bioavailability. The process involves the precipitation and agglomeration of crystals to produce spherical agglomerates. The precipitation is achieved by adding an anti-solvent to a good solvent in which the drug is dissolved, and the agglomeration is achieved by addition of a bridging liquid (binder liquid) which is immiscible in mother liquor [1].

Currently, there is no mechanistic understanding of all the rate processes occurring with regard to the primary crystals until the formation of spherical agglomerates. However, based on the similarity between wet granulation and spherical agglomeration, the following rate processes may be proposed: wetting/nucleation of primary crystals by the bridging liquid, consolidation/growth of agglomerate nuclei, and attrition/breakage of the agglomerates [2-3]. The aim of the current study is to identify the influence of key material properties (e.g. surface energy) and process parameters (e.g. shear rate) on the final properties of agglomerates (e.g. size, porosity). This can be achieved by a) integration of different targeted, systematic small scale experiments, and b) implementation of computer-aided process design tools such as population balance modelling.

Spherical agglomeration experiments were conducted in a stirred vessel and an oscillatory baffled reactor. A novel microfluidic system and a contracting nozzle device were proposed and devised to respectively investigate wetting/nucleation, and attrition/breakage of the agglomerates in isolation. gPROMS FormulatedProducts® was used to develop a population balance model for the agglomeration in suspension process which included a customised agglomeration kernel. The predicted results of the model were compared with the experimental data and the effect of material properties and process conditions on the wetting/nucleation and attrition/breakage phases, as well as size distribution of the produced agglomerates, was determined through the experiments and the developed model.

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[2] J. D. Litster, Design and processing of particulate products, Cambridge University Press, (2016).

[3] K. Pitt, P. Ramon, J.D. Tew, K. Pal, R. Smith, Z.K. Nagy, J.D. Litster, Particle design via spherical agglomeration: A critical review of controlling parameters, rate processes and modelling, Powder Technology, 326 (2018) 327-343.

65. EFFECTS OF MATERIAL TYPES AND OPERATING CONDITIONS ON PROPERTIES OF PARTICLES PRODUCED WITH PULSE COMBUSTION DRYING

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Pulse combustion drying as a novel technology has been applied for production of powders from different types of materials. The process was shown able to produce particles with narrower size distribution and better properties. In this technology, the solution (or suspension) to be dried is sprayed into a pulsating gas flow created by a pulse combustion unit. It has been found that smaller droplet size could be achieved with lower feed rate, moderate viscosity, and higher flow oscillation [1]. As the droplets are in contact with surrounding gas, the solvent (water) evaporates and solid particles are obtained as the final product. The final particle size and morphology are determined by how fast solvent evaporation is compared to solute diffusion towards the droplet centre, and by some additional phenomena that may occur during the process, such as inflation-deflation and breakup. The additional phenomena depend on the type of solute materials and how their properties change during the process. The whole process is thus very complex and is a function of many interacting variables. While studies on product properties are common for the case of conventional spray drying [2], very few could be found for pulse combustion drying. In this study, experiments are carried out to investigate the influence of material types and operating conditions of a pulse dryer on final particle properties. Three types of solutes at varied concentrations are used: silicon dioxide, sodium benzoate, and maltodextrin, which represent water-insoluble, water-soluble, and sticky solute materials, respectively. Variations of feed rate, drying gas temperature, average velocity, and pulsation frequency are employed. The size distribution of produced particles is measured with particle size analyser, and the morphology is examined with scanning electron microscopy.

[1] Z. Xiao, X. Xie, Y. Yuan, X. Liu, Influence of atomizing parameters on droplet properties in a pulse combustion spray dryer, Drying Technology, 26 (2008) 427-432.

[2] C. Turchiuli, A. Gianfrancesco, S. Palzer, E. Dumoulin, Evolution of particle properties during spray drying in relation with stickiness and agglomeration control, Powder Technology, 208 (2011) 433-440.

66. THE INFLUENCE OF LIGNIN ON API CONTENT UNIFORMITY IN CONTINUOUS TWIN-SCREW WET GRANULATION PROCESSES

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The pharmaceutical industry is under pressure to move from a conventional batch wise to continuous processing. In the pharmaceutical industry, content uniformity of drug is a key quality attribute in oral solid-dosage formulations. The non-uniformity of drug content may affect drug release during the dissolution stage [1-3].

The wet granulation process is a common granulation method, which involves high shear mixer granulation, hot melt extrusion, twin-screw granulation and fluidized-bed granulation. The use of twin-screw granulation (TSG) as a continuous wet production technique is increasing in the pharmaceutical industry sector due to reduced operational cost, shorter lead times, and better process control. Therefore, the aim of this study is to investigate the content uniformity of active pharmaceutical ingredient (API) and granule behaviour during the twin-screw wet granulation process. Two different formulations were considered, the first formulation contained acetaminophen as API and microcrystalline cellulose (MCC 101) as excipient, and the second formulation contained acetaminophen as API, MCC 101 with lignin as excipient. The main objective was to study the effect of lignin on granule behaviour and API content uniformity. For these experiments, two operation variables were considered, i.e. liquid to solid ratio and screw speed. API content uniformity is determined through sieve analysis and solubility measurements. Feed flow rate was kept constant.

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[2] S. Oka, H. Emady, O. Kaspar, V. Tokarova, F. Muzzio, F. Stepanek, R. Ramachandran, The effects of improper mixing and preferential wetting of active and excipient ingredients on content uniformity in high shear wet granulation, Powder Technology, 278 (2015) 266-277.

[3] H. Alyami, E. Dahmash, J. Bowen, A. R. Mohammed, An investigation into the effects of excipient particle size, blending techniques and processing parameters on the homogeneity and content uniformity of a blend containing low-dose model drug, PLOS ONE, 12 (2017) e0178772.

67. MODEL-DRIVEN SCALE-UP FRAMEWORK FOR HIGH-SHEAR WET GRANULATION

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Wet granulation processes are difficult to scale up because conventional methods require ample experimental data to determine the most favourable operating conditions. A systematic model-driven framework can facilitate this scale-up process by reducing the number of experiments required. Therefore, an appropriate model is required which should be developed based on a good understanding of all major wet granulation mechanisms. Such a model can give a better insight into the process and the effects of the experimental conditions on the granulation end point which is needed for process design and scale-up studies.

In this study, a model-driven scale-up framework is proposed and applied to a high-shear wet granulation process. A compartment-based model is applied employing a one-dimensional population balance framework. The wet granulation mechanisms are represented by rate expressions which are based on mechanistic understanding. Unknown parameter values are measured, simulated or estimated using experimental data and finally, the model is validated using experimental data at different process scales. Different compartmentalisation approaches are developed and assessed based on their ability to predict experimental results.

68. COMPARATIVE GRANULATION OF A PHARMACEUTICAL FORMULATION USING DIFFERENT GRANULATION TECHNIQUES

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2 Alexanderwerk GmbH, Kippdorfstraße 6-24, 42857 Remscheid, Germany
3 Romaco Kilian GmbH, Scarletallee 11, 50735 Köln, Germany
4 Romaco Innojet GmbH, Daimlerstraße 7, 79585 Steinen, Germany
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Granulation is a fundamental process in the pharmaceutical and other industries to convert powders of poor flow and compressibility into agglomerates. These agglomerates feature improved flow, compressibility and uniformity which is required for example in tablet compression.[1]

This work describes the granulation of an immediate release formulation with paracetamol as model API, low-substituted hydroxypropyl cellulose (L-HPC) as disintegrant, polyvinyl alcohol (PVA) as granulation binder and lactose as filler. The formulation was processed using four different granulation technologies; in particular wet granulation with a high shear mixer, fluid bed granulation, twin screw granulation, and dry granulation by roller compaction. Granules were blended with magnesium stearate and subjected to tablet compression on a compaction simulator.

Granules CQAs (bulk density, particle size, SEM micrographs) are discussed together with processing and formulation parameters which change the properties of granules. After compression into tablets, the tensile strength, solid fraction, disintegration time and dissolution of compacts is analysed. These attributes vary depending on the granulation technology when the identical formulation is processed. However the compression of granules into tablets yielded tablets with tensile strength >2 MPa at 200 MPa compaction pressure regardless of the granulation technology used (>1.7 MPa acceptable for production [2]).

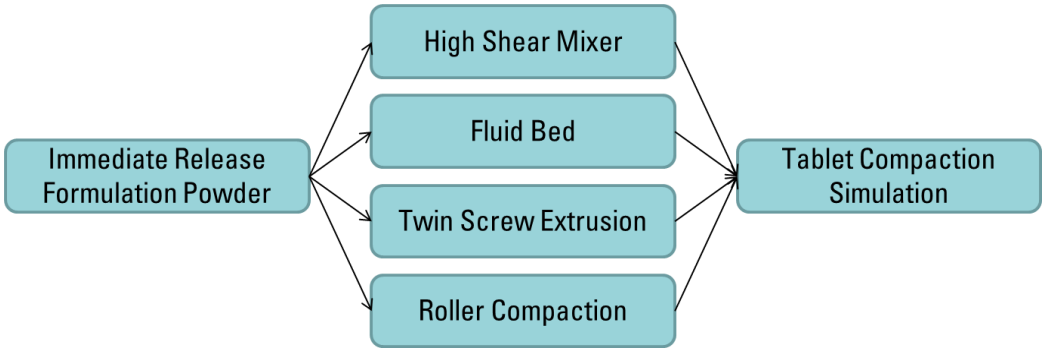

Figure 1. Schematic of particle processing using different technology

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69. PROTEIN–POLYPHENOL MULTILAYER MICROCAPSULES FOR ORAL DELIVERY OF BIOLOGICALLY ACTIVE COMPOUNDS IN FUNCTIONAL FOODS

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Functional foods contain biologically active compounds providing health benefits beyond basic nutritional functions and may be consumed as part of regular diet. However the health benefits of various biologically active compounds (e.g. probiotics and prebiotics, functional proteins and peptides, some vitamins and polyphenols) are negated by the effects of stomach digestion and poor targeting to the lower gastrointestinal tract (GIT), which is often required for efficacy. Therefore, a number of approaches to overcome this challenge have been developed over the past decade. They involve chemical modification of bioactive compounds to make them less susceptible to stomach digestion, and microencapsulation, e.g. in liposomes, Ca-alginate or sodium caseinate micro-gel particles. The major drawbacks of all these systems are the use of organic solvents and harsh encapsulation conditions that may result in a significant loss of bioactivity. In this work we present a simple encapsulation system for oral delivery of bioactive compounds using layer-by-layer assembled protein-polyphenol microcapsules made of low-cost and food grade ingredients [1]. A high value functional whey protein, Lactoferrin (Lf), is used here as a model bioactive compound. Encapsulation provides: effective protection from gastric digestion; enhanced adhesion towards intestinal surface; control over the release rate; enhanced bioavailability.

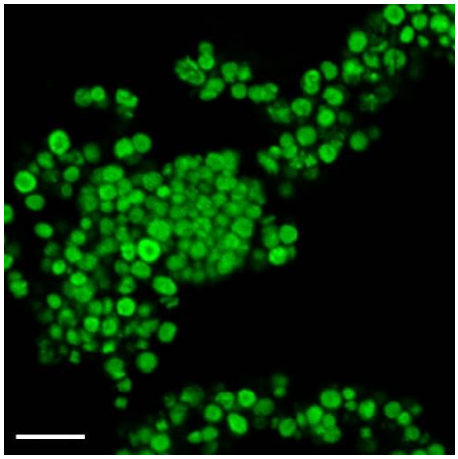

Figure 1. Confocal laser scanning microscope image of (Pepsin-tannic acid)$_4$ capsules, scale bar 10 μm.

[1] H.H. Lau, R. Murney, N.L. Yakovlev, M.V. Novoselova, S.H. Lim, N. Roy, H. Singh, G.B. Sukhorukov, B. Haigh, M.V. Kiryukhin. Protein-tannic acid multilayer films: a multifunctional material for microencapsulation of food-derived bioactives, Journal of Colloid and Interface Science, 505 (2017) 332–340.

70. NOVEL ALGORITHM FOR PARTICLE TRACKING VELOCIMETRY (PTV) OF NON-SPHERICAL PARTICLES

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Non-spherical particles are commonly encountered in industrial applications, for instance, tablet coating in Wurster fluidized bed. Knowledge about the influence of particle shape on particle motion is essential for process design and optimization. However, measurements of non-spherical particle dynamics, even in a pseudo-2D bed, are very difficult due to the anisotropic drag forces and anisotropic collisions. As shown in Figure 1, a new PTV method for non-spherical particles was developed and verified based on synthetic images generated from DEM simulation of super-quadric particles (rod-like and tablet) [1]. Single particle calibration including both, area and aspect ratio, was conducted to identify the orientation. Analogously to color-PTV measurement [2], the particles are randomly coloured with three colours in synthetic images to effectively reduce the influence of overlaps on particle segmentation. The watershed transform was used to separate slight overlaps. The novel methodology shows good performance in reconstructing translational and rotational velocities of non-spherical particles for solid volume fraction lower than 0.2.

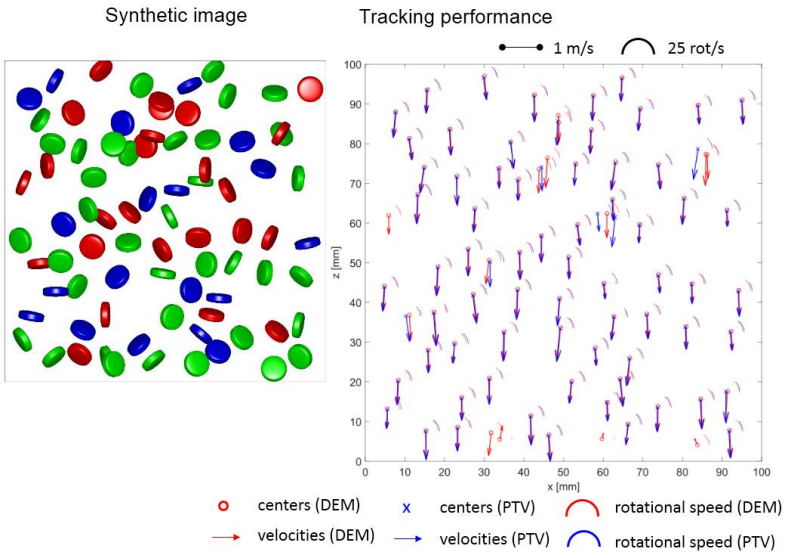

Figure 1. Particle tracking velocimetry (PTV) for tablet particles

[1] A. Podlozhnyuk, S. Pirker, C. Kloss, Efficient implementation of superquadric particles in Discrete Element Method within an open-source framework, Comp. Part. Mech. 4 (2017) 101–118.

[2] Z. Jiang, T. Hagemeier, A. Bück, E. Tsotsas, Color-PTV measurement and CFD-DEM simulation of the dynamics of poly-disperse particle systems in a pseudo-2D fluidized bed, Chemical Engineering Science. 179 (2018) 115–132.

71. PARTICLE SIZE MEASUREMENT IN ROTARY FLUIDIZED BED WITH STATISTICAL DESIGN

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In-line particle size measurement with spatial filter velocimetry probe (SFV, Parsum, Chemnitz) for process control was already carried out successfully in fluidized bed granulation and coating [1] but was not investigated in rotary fluidized bed agglomeration and tangential spray process for pellet manufacturing yet.

A batch laboratory fluidized bed apparatus with rotor insert (GPCG 1.1, Glatt, Binzen) was used. The SFV probe was installed above the rotor plate. Particle size and particle size distribution of mixtures of small and large pellets (Cellets®200 and Cellets®1000, x50,3 = 250 and 1170 µm, respectively) were measured directly in the tangential rotary fluidized bed over 10 min without spraying. The content of large pellets in the mixtures was 1%, 2.5%, 5% and 10 % (w/w). Volume and number based density and cumulative distributions as well as median are calculated by the probe´s software every two seconds during the process. The volume density distribution at the end shows bimodal curves (Figure 1). The peak height at 1170 µm increases with increasing content of Cellets®1000, whereas the peak height at 250 µm decreases. Higher Cellets®1000 peaks compared to Cellets®200 result from stronger influence of large particles in the volume density distribution.

Furthermore, microcrystalline cellulose powder was agglomerated with binder solution (polyvinylpyrrolidone, polyethylene glycol and sodium benzoate) in a rotary fluidized bed granulation process with tangential spray. Process limits were determined. A Placket-Burman screening design identified critical process parameters by measuring particle size and particle size distribution. SFV probe can be used in process control of rotary fluidized bed granulation.

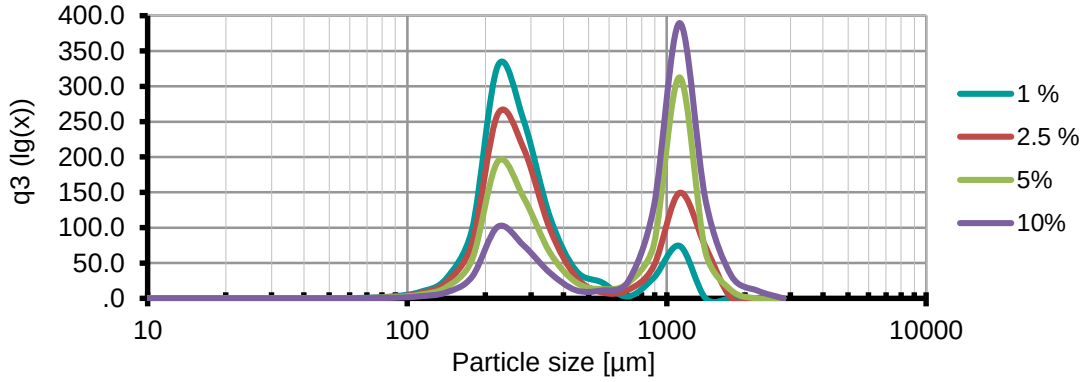

Figure 1. Volume density distribution q3 (lg(x)) of mixtures of Cellets®200 with increasing Cellets®1000 content

[1] Wiegel, D., Eckardt, G., Priese, F., Wolf, B.: In-line particle size measurement and agglomeration detection of pellet fluidized bed coating by Spatial Filter Velocimetry. Powder Technology 301 (2016) 261-267.

72. A ROBUST SYSTEMS FRAMEWORK FOR MODELLING A TABLET MANUFACTURING PROCESS

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Process system modelling, or flowsheet modelling, is an established approach in the processing industries for fluids based processes. More recently, it is emerging as a tool for solids based processes, as mechanistic models for distributed particulate materials become more available. Access to this type of modelling presents significant opportunities for traditional pharmaceutical process development. In this example, a tablet manufacturing process has been assembled in modular fashion within the gPROMS FormulatedProducts (v 1.2, Process Systems Enterprise Ltd.) software package. Implementation and use of this tool has been used to facilitate process development within an actual industrial setting.

Each unit operation has been mechanistically modelled from first principals, and subsequently refined and validated using process data. The manufacturing processes incorporated within the simulation include: roller compaction, milling and the tablet press.

Constructing the system model within the software has provided a useful guide for identifying knowledge gaps that need to be addressed via laboratory and/or pilot scale experimentation. It has also provided a convenient repository for capturing the quantitative data generated by the physical trials.

Once the model was complete it was then possible to investigate the process in holistic fashion entirely in-silico. This allowed the design space to be thoroughly, and rapidly examined and parameter set-points and ranges deduced. It is therefore envisioned that a similar methodology could be adopted whenever similar processes need to be developed.

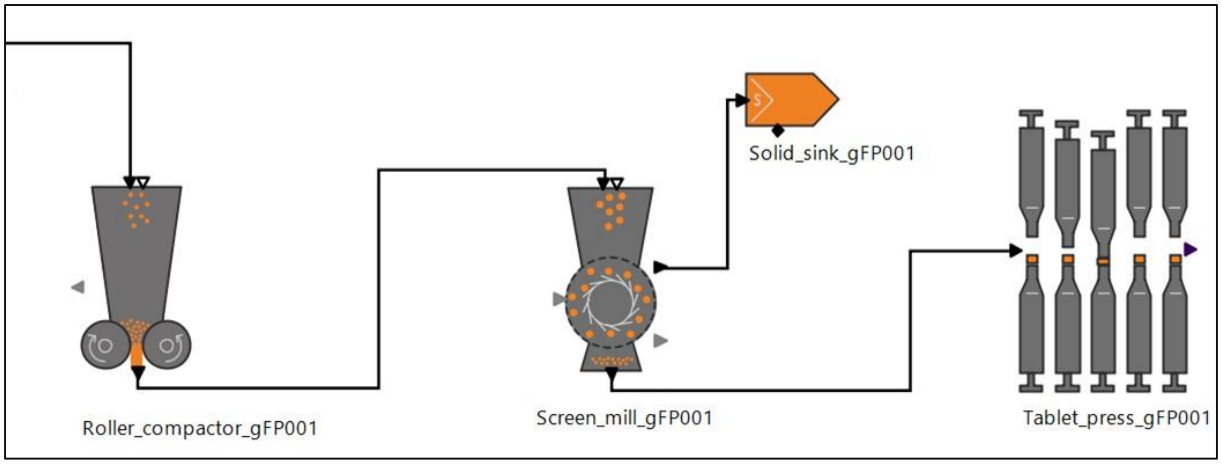

Figure 1. The drag and drop flowsheet used to model the tablet manufacturing process in gPROMS FormulatedProducts.

73. EFFECT OF CHEESE AGE AND ADDITION OF DAIRY INGREDIENTS ON WETTABILITY, DISPERSIBILITY AND TOTAL REHYDRATION OF CHEESE POWDER

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Cheese powder is an important multifunctional ingredient used to provide taste, mouthfeel, and appearance as well as for improvement of texture in various food formulations [1]. Reconstitution properties of cheese powders are important to assure homogeneity and functionality within a given food system. Cheese type and composition (e.g., degree of maturation, fat and protein content), as well as the addition of emulsifying salts (ES) during cheese powder manufacture, can strongly affect the final cheese powder properties [2,3]. The reconstitution properties of cheese powders without ES have not been previously investigated. We have therefore investigated the effect of the addition of dairy ingredients (2% sodium caseinate plus 2% buttermilk powder (B2S2) or 4% buttermilk powder (BMP)) as alternative to the used of ES, as well as the use of cheeses with different age (16, 30 or 45 weeks old) on wettability, dispersibility and total rehydration. B2S2 cheese powders showed increased wettability, whereas its dispersibility has been delayed showing bigger particles in solution after dissolution. Contrary, powders containing only BMP as well as powders produced with 45 weeks old cheese presented faster dispersibility. Reconstituted powders (1:1 w/w) produced with 16 weeks old cheese lacked the most mobile water component (analyzed by low-field nuclear magnetic resonance), compared to the other powders, indicative of better total rehydration. Measurements of total solubility and water holding capacity based on total solids quantification after reconstitution were not found to be suitable for evaluating the reconstitution properties of cheese powder. In conclusion, the study provided information of the reconstitution properties of cheese powders and can provide basis information for the future tailored production of cheese powders with improved rehydration properties.

[1] Z. Erbay, N. Koca, Effects of whey or maltodextrin addition during production on physical quality of white cheese powder during storage, J. Dairy Sci. 98 (2015) 8391–8404.

[2] D. Felix da Silva, F.H. Larsen, A.B. Hougaard, R. Ipsen, The influence of raw material, added emulsifying salt and spray drying on cheese powder structure and hydration properties, Int. Dairy J. 74 (2017) 27–38.

[3] D. Felix da Silva, L. Ahrné, F.H. Larsen, A.B. Hougaard, R. Ipsen, Physical and functional properties of cheese powders affected by sweet whey powder addition before or after spray drying, Powder Technol. 323 (2018) 139–148.

74. SPRAY-DRYING ENCAPSULATION OF LACTIC ACID BACTERIA IN POWDERS WITH TEMPERATURE-DEPENDENT SOLUBILITY BY CONTROL OF ENZYMATIC MILK CLOTTING

Justine Guérin[1], Jeremy Petit[1], Jennifer Burgain[1], Frédéric Borges[1], Bhesh Bandari[2], Stéphane Desobry[1], Joël Scher[1] & Claire Gaiani[1,2]

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This study intended to develop a water-insoluble matrix to encapsulate *Lactobacillus rhamnosus* GG, a probiotic bacteria, by spray-drying. For this purpose, it was taken advantage of the clotting reaction of dairy proteins. The feed solution was composed of probiotic bacteria and dairy proteins that were subjected to the action of chymosin, a proteolytic enzyme. The influence of outlet air temperature (55, 70, and 85 °C) on microencapsulation efficiency was investigated. All spray-drying conditions led to excellent bacterial survival rates (< 0.5 log reduction), whereas only an outlet air temperature of 85 °C allowed the production of microparticles with suitable moisture content (< 7 %) to ensure storage stability. Then, the water reconstitution properties of these microparticles were evaluated at 8 and 40 °C. At 40 °C, microparticles were unable to rehydrate, they remained compact and their solubility was low, hence bacteria stayed embedded. At 8 °C, powder rehydration occurred, releasing probiotic bacteria in the medium. This temperature-sensitive reconstitution behaviour resulted from the decoupling of the enzymatic action of chymosin and the non-enzymatic casein network formation. First, the enzymatic reaction occurred in the feed solution maintained at 4 °C prior to the spray-drying process. Interactions between clotted caseins occurring only over 10 °C, the casein micelle network formation was avoided during spray-drying. Reconstitution in warm water allowed casein network formation, precluding microparticle solubilisation, hence ensuring the protection of encapsulated bacteria. On the contrary, reconstitution in cold water allowed releasing bacteria, which could be interesting for revivification purposes in the ferment industry.

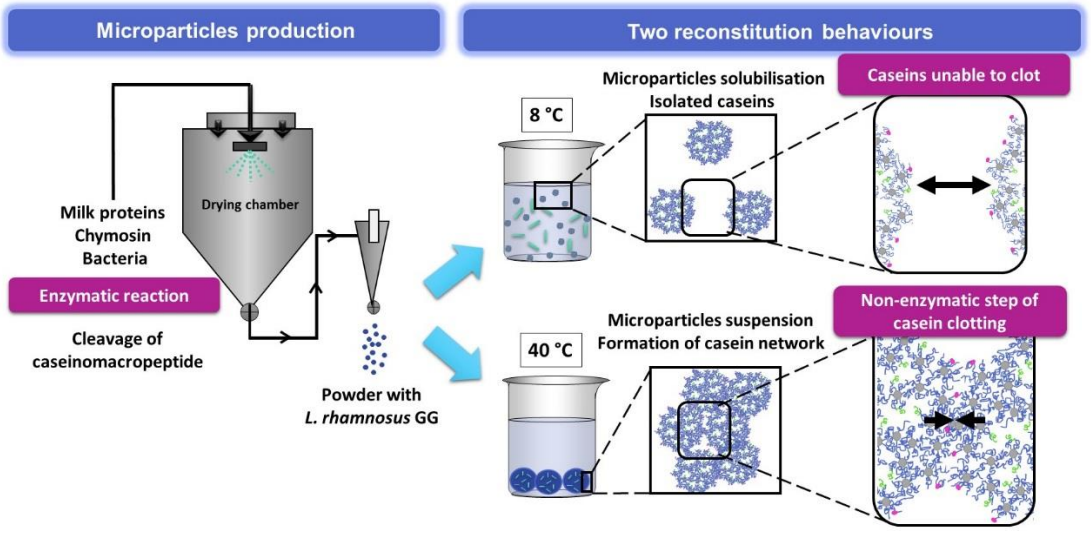

Figure 1. *L. rhamnosus* GG encapsulation by spray-drying, leading to a temperature-dependent reconstitution behaviour.

75. DRYING OF NANOSUSPENSION USING ELECTROSPRAYING TECHNIQUE: EFFECT ON POWDER RECONSTITUION

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Electrospraying is emerging as unique method for producing monodisperse micro and nanoparticles with porous characteristics due to immediate solidification of drug. In this method a liquid stream of drug polymer solution is sprayed under the influence of electric force through a fine capillary, resulting in fine droplets which are deposited on grounded collector plate. Various modifications in conventional setup of electro spraying has been done in terms of solution sprayed, number of needles used for spraying, distance between needle and collector plate, voltage applied, collector plate setup, etc. to obtain dry powder with desirable particulate and bulk level properties. In present work, we have prepared BCS class-II drug nanosuspension and modified the bulk properties of the electrosprayed nanosuspension obtained, by including varying ratios of polyols and sugars in it.

The obtained electro sprayed powder was characterized for various solid state properties using techniques like differential scanning calorimetry (DSC), X-ray diffraction (XRD), particle size distribution, Fourier Transform Infra-Red (FTIR), wettability, scanning electron microscopy, porosity surface area analysis and saturation solubility. The results revealed that the solubility advantage of nanosuspension was retained upon electrospraying and the obtained powder showed fair bulk level properties. Orally dispersible dosage forms prepared using electro sprayed powder showed retention of modified properties as imparted during electrospraying process.

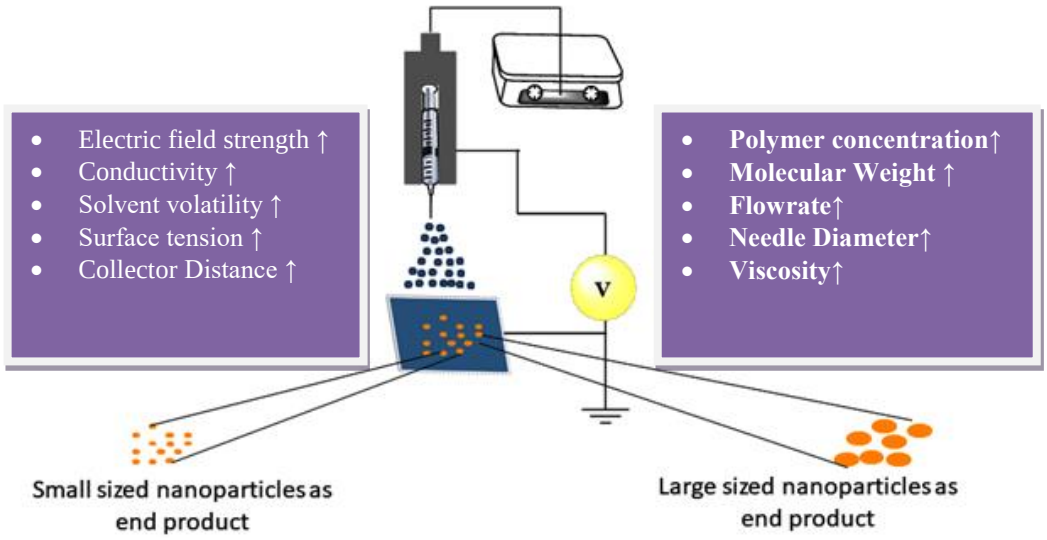

Figure 1. showing effect of various Critical process parameters and critical material attributes affecting electrosparying

[1] A Pawar, S. Thakkar, M. Misra. A bird's eye view of nanoparticles prepared by electrospraying: advancements in drug delivery field, Journal of Controlled Release, 286, 179-200, (2018).

76. THERMAL METHODS: HOW ACCURATELY THEY CAN BE USED FOR ASSESSMENT OF MIXING UNIFORMITY

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The mixing of powders and granular material is of central importance for producing quality and performance of a product. Assessing mixing uniformity of the powder blend in the pharmaceutical formulation of a low dose potent drug is a very critical step in pharmaceutical solid orals. Thermal analytical method like differential scanning calorimetry (DSC) and hotstage microscopy are rapid, require very less sample for quantification and can be included in preformulation and formulation processes.

In this project we have used enthalpy values obtained from DSC for estimation of mixing uniformity in powder blend, mixed using high shear mixture granulator and tried to establish a correlation between the results of DSC and High Performance Liquid Chromatography method. Hot stage microscopy was further used to confirm the results obtained and to quantify the particle size of API in the given blend. Blends with varying percentage of drug were prepared to further validate our results. Results of DSC, Hot stage microscopy and HPLC revealed that at 3% levels of drug present in blend, the results obtained from all three techniques were corroborating, however at levels below this, the accuracy of results was not very reliable. However considering the advantages of the low sample requirement, almost no need for sample preparation technique and instantaneous result which are obtained using thermal methods, they could emerge as potential replacement to conventional methods.

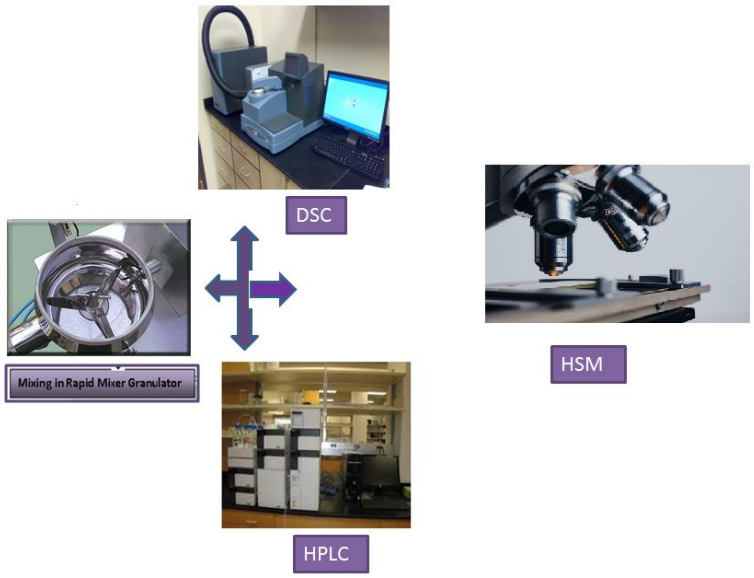

Figure 1. Co-relating mixing uniformity using thermal methods and HPLC.

[1] E Bharvada, V Shah, M Misra. Exploring mixing uniformity of a pharmaceutical blend in a high shear mixture granulator using enthalpy values obtained from DSC, Powder technology 276 (2015) 103-111.

77. EFFECTS OF BINDER ADDITION ON THE TABLET QUALITY ATTRIBUTES OF A NOVEL AMORHPOUS SOLID DISPERSION

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Direct compression is the method of choice in the manufacturing of tablets due to its fewer processing steps in comparison to other methods and the absence of process induced heat and moisture effects [1]. Given the absence of pre-processing steps in direct compression, material properties and processing conditions directly affect the quality and reproducibility of tablets.

This study seeks to investigate critical quality attributes such as tablet disintegration, tablet friability and the mechanical strength of compacted formulations at varying ratios. Formulations comprise a hot melt extruded amorphous solid dispersion (ASD) of a poorly water-soluble drug loaded onto a porous carrier and a novel multifunctional performance excipient - both developed in-house. The prepared ASD was characterised in terms of its particle strength using the Kawakita equation in order to determine the upper limit of the compaction pressure before a collapse of the carrier matrix of the ASD may occur. The compaction pressure of the tableting machine for prepared formulations was subsequently chosen to be below the determined upper limit.

[1] Jivraj, M., Martini, L. G. & Thomson, C. M. An overview of the different excipients useful for the direct compression of tablets. Pharmaceutical Science & Technology Today, 3 (2000) 58-63.

78. EVALUATION OF AN ELECTRONIC GAMLEN GTP-1 PRESS TO MEASURE AND COMPARE COMPRESSIBILITY OF HE POWDER

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A bench-top, 500 Kg load cell GTP-1 press was evaluated as a reliable tool to perform routine measurement and comparison of a key compressibility parameter (Yield Pressure, Py) of high explosive (HE) powders. The method was first developed by comparing the in-die Heckel derived - Py values of two inert micrometric powder standards (pharmaceutical grade Ibuprofen and microcrystalline cellulose PH-101 Avicel) with the corresponding literature values. Heckel plots were obtained by analysing real-time in-die compression load/displacement profiles before and after correction for (internal) elastic compliance. Following validation of the standards, the method was successfully applied to compare compressibility of four batches of 1,3,5-Triamino-2,4,6-trinitrobenzene (TATB) of different origin (US and UK).

79. IMPACT OF FORMULATION ON THE RECONSTITUTION PROPERTIES OF SPRAY-DRIED DAIRY POWDERS

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On one hand, this study focuses on the impact of fat content (1.5, 13.8, and 26 % (w/w)) and air incorporation in concentrates. On the other hand, the influence of the whey protein/casein ratio (100/0, 79/21, 57/43, 35/65, and 12/88) on the characteristics of dairy protein powders was investigated. Spray-drying conditions were as follows: 200 °C inlet air temperature and 85 °C outlet air temperature. Physicochemical properties (particle size distribution, shape factors, moisture content, water activity, and surface composition by XPS) of spray-dried powders were characterized in view to explain their rehydration properties, evaluated by the solubility (ISO 8156 : 2005), wettability (FIL 87 : 1979), and dispersibility (FIL 87 : 1979) indices.

The first part of the study revealed that changing the fat content induced no significant difference of powder solubility, as mean particle size of fatty powders was increased, thus counteracting the negative effect of powder surface hydrophobicity. It was also shown that air incorporation in feed concentrates did not affect rehydration properties, even though surface fat and mean particle size were decreased (Figure 1). The second part of the study permitted to evidence that solubility of dairy protein powders linearly varied with the whey protein/casein ratio (Eq. (1), R^2 = 98.62 %):

$$Solubility\ (\%) = 99.554 - 0.698 \times casein\ content\ (\%) \qquad \text{(Equation 1)}$$

Last, it was highlighted that the wettability and dispersion indices were not relevant to evaluate the rehydration ability of investigated powders. In fact, all studied powders were non-wettable and non-dispersive according to the milk powder standards, owing to the low mean particle size (between 10 and 30 µm) of powders produced by spray-drying at pilot-scale.

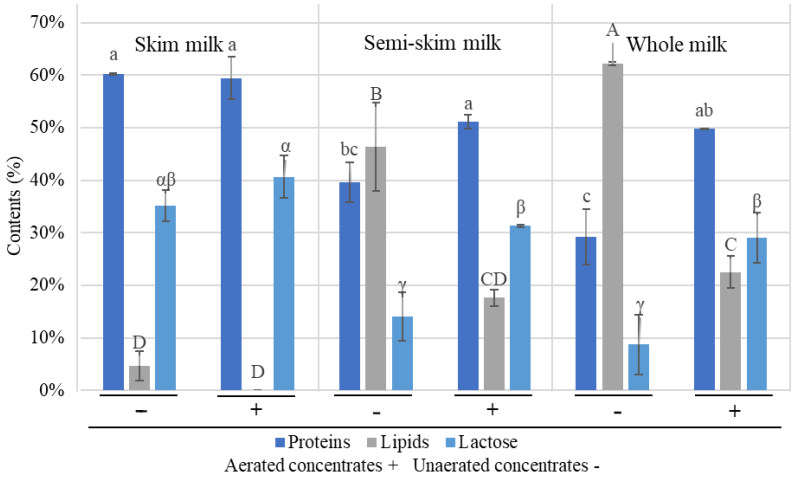

Figure 1. Surface composition deduced from XPS analysis of skim, semi-skim, and whole milk powders with or without aeration of concentrate prior to spray-drying. Bars topped with different letters correspond to significantly different results ($p < 0.05$, $n = 2$).

80. AERODYNAMIC GRANULATION SYSTEM - A CONTINUOUS, CLOSED, DRY GRANULATION PROCESS FOR PHARMA, FOOD & CHEMICAL SUBSTANCES

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The Aerodynamic Granulation System (EU PAT 2364183; US PAT 8,590,818 B2) is a technology designed to produce granules in dry conditions through a continuous process, inside a plant set to operate with a suitably defined gas stream. AGS can be used for pharmaceutical, food and chemical substances. The method can generate raw materials with enhanced properties, such as 1) powder surface engineering (e.g. enhancement of the powder flowability); 2) increased bio-availability; 3) homogenous end-product (shape of particles, particle size distribution, surface roughness, etc) [1]. The granulation process is continuous, fast and is run in a fully closed system, employing either air or inert gases. Additionally, the AGS method offers several advantages especially economic and operating. The system, in fact, does not need water, high temperatures or additives to operate, with remarkable savings in terms of energy, inputs, waste and cleaning times.

AGS works thanks to a continuous vigorous airflow stream throughout the whole process. The final quality of the granule is dependent on the characteristics of the air/gas flow and on the quality of the gas employed. The key variables of the AGS process are: the airflow rate; the compactor rolls force; the sieve size and rotation speed of the main ribbon crusher; the rotation speed of the fractionator device. The AGS technology is structured as shown in the following Figure 1: 1) the starting material is lifted from the feeding bin to the roller compactor where it is compressed between two rotating rolls to a more or less continuous ribbon; 2) the ribbon is then broken down to granules of a suitable size using rougher or finer sieves and then processed through a mill; 3) the fractionator unit separates granules from the finer fraction and selected granulated material is then collected in a bin. 4) The fraction of fines is extracted by a cyclone and recirculated into the system for an additional granulation step.

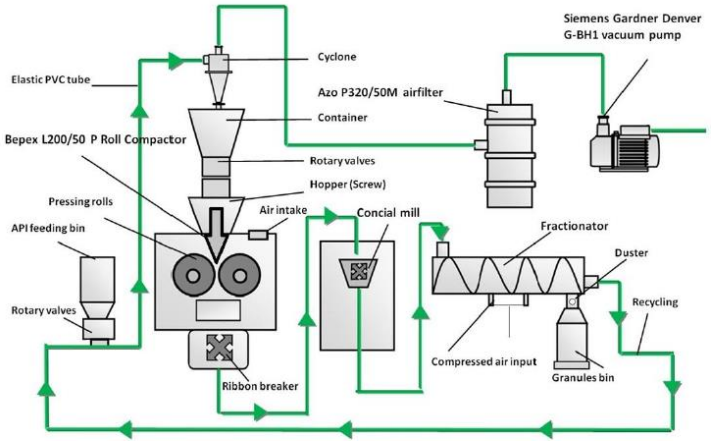

Figure 1: Aerodynamic Granulation System – Process Chart

[1] T. Saarinen, J. Yliruusi, Final report: Proof of concept project, University of Helsinki - Faculty of Pharmacy, (2015) 2-4.

81. ROLL COMPACTION NIP REGION SCALE-UP PARAMETERS SUPPORT MATHEMATICAL PREDICTION METHODOLOGIES

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Roll compaction is a dry granulation process highly dependent on material characteristics, equipment design and operating parameters [1]. Feeding rates, roll pressure, roll speed, roll surface, nip region and gap control being common equipment variables optimized when making a ribbon or compact [2,3]. The challenge often derives when transitioning from lab-scale to a production environment and ensuring the end product has the same properties developed in the lab [4].

This work focuses on addressing the challenges derived when transitioning roll compaction results from lab-scale to a production environment. In particular, it looks at the critical need to maintain roll compactor's nip angles constant during the scale up process. It also validates the importance of nip region geometry when producing ribbons with as little as 10 grams and still be able to transfer the operating parameters to larger scale equipment

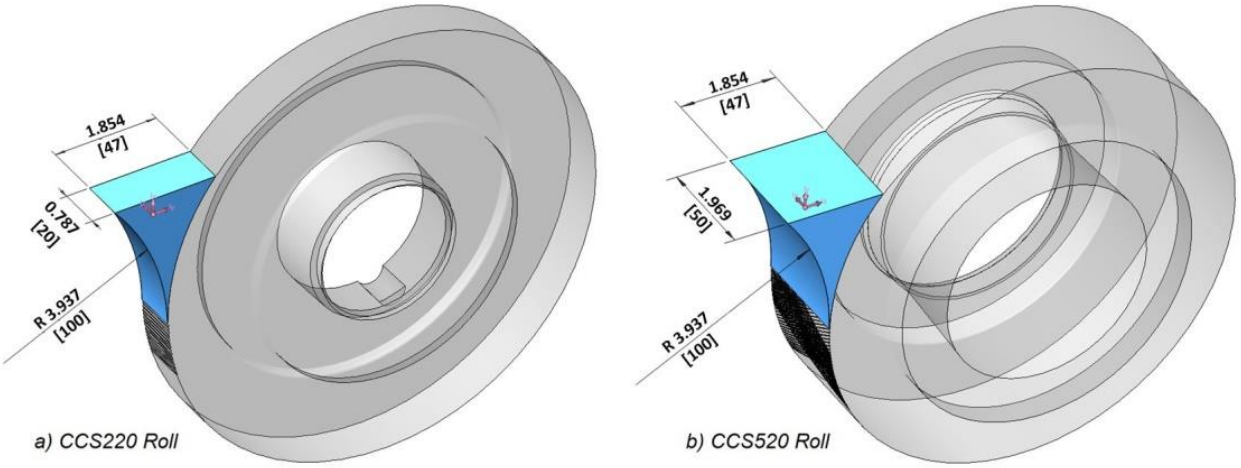

Figure 1. Lab vs. Production Machines' Nip Region Volumes

[1] G. Bindhumadhavan, M.J. Adams, R.W. Greenwood, S. Fitzpatrick, Roll Compaction of Pharmaceutical Excipients: Experimental Validation of Rolling Theory for Granular Solids. Chemical Engineering Science, 60 (14) (2005) 3891-3897

[2] S. Yu, Roll Compaction of Pharmaceutical Excipients, Doctor of Philosophy Thesis, School of Chem. Eng. College of Engineering, The University of Birmingham (2012)

[3] E. Hadzovic, Roller Compaction of Theophylline, Inaugural Doctoral Dissertation, Univ. of Basel (2008)

[4] Z. Liu, M.J. Bruwer, J.F. MacGregor, S.S.S. Rathore, D.E. Reed, M.J. Champagne, Scale-up of a Pharmaceutical Roller Compaction Process Using a Joint-Y Partial Least Squares Model, I&EC Research, Ind. Eng. Chem. Res., 50 (2011) 10696-10706

82. ADVANCES IN PARTICLE SIZE DISTRIBUTION PREDICTABILITY – BRIDGING THE EXPERIMENTAL GAP

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For decades, determining the operating parameters of a conical size reduction machine in order to attain a specific particle size distribution (PSD) has been achieved largely through trial-and-error. This is mainly due to what governs particle size reduction: 1) the characteristics of particles (their fracture mechanics, material properties, granulation methods, etc.) and 2) the milling equipment selected and its set up. Over the years, several size reduction theorems have been proposed [1]. Unfortunately, these formulas are difficult to apply to conical milling partly due to oral solid dosage formulations being composed of agglomerates [2]. One impact attrition model (Ghadiri and Zang [3]) predicts volumetric wear rate depends on granule size and a mill's impeller speed squared, but does not take into account other equipment variables.

This work focuses on the development of a PSD predictive formula for a conical size reduction mill by including all key equipment variables, such as impeller and screen selections and used a Design of Experiments (DoE) approach. Findings from the empirical DoE tests were compared to the predictive theorem and results were found to be within acceptable high and low range limits.

$$d_t \propto \frac{H_r \left(\frac{T_s}{U}\right)^2 d_g \, H \, S_f \, I_f \, F_f}{K_c^2}$$

$$S_f = S_d \; S_p \; S_{oa}$$

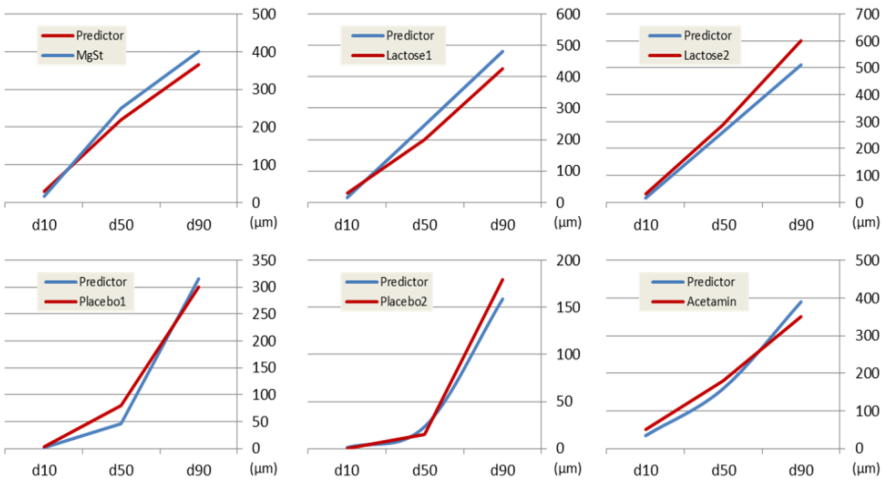

Figure 1. PSD Comparisons Between Empirical Data and Theoretical PSD Predictor Formula

[1] S.R. Gurvinder, V. M.K. Vuppala, Sizing and Granulation, Handbook of Pharmaceutical Granulation Technology, Chapter 13 (1997)

[2] D. Parikh, G.V. Rekhi, M.K. Vuppala, Handbook of Pharmaceutical Granulation Technology. Chapter 13 (1997)

[3] M. Ghadiri, Z. Zang, Impact Attrition of Particulate Solids. Part 1. A Theoretical Model of Chipping. Chem. Eng. Sci. 57 (2002) 3659–3669

83. FEEDBACK CONTROL OF FLUID BED GRANULATION USING REAL-TIME PARTICE SIZE MEASUREMENT

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Fluid bed granulation is a widely used and common process in the pharmaceutical industry. Real-time measurements of critical quality attributes, such as particle size, provide a promising approach for feedback control driven process automation of fluid bed granulation to ensure high product quality (Figure 1, left). Hereby, a control variable is compared to predefined set point. By adapting a predefined process variable, the controller maintains the controlled variable at the predefined set points (Figure 1, right). Madarasz et al. [1] recently described a successful approach of real-time feedback control for twin screw granulation based on image analysis.

This work focused on the implementation of a feedback control system using spatial filtering technique for real-time particle size measurement with an integrated modified time-based particle buffer system during fluid bed granulation. Therefore, a PI controller was implemented using the atomization air pressure (process variable) as corrective action. The implemented control system should achieve a predefined target particle size (controlled variable) after spraying a specific amount of spraying solution by following a target particle size curve. Firstly, the optimum controller settings were defined by testing different K_p and K_i tuning parameters, in order to provide best performance of the control system. Secondly the functionality of the implemented control system was evaluated by increasing and decreasing the target particle size as well as differing target particle size curves. Furthermore, the robustness was investigated by varying process and formulation parameters. Results demonstrated suitable functionality as well as acceptable robustness for the described control system.

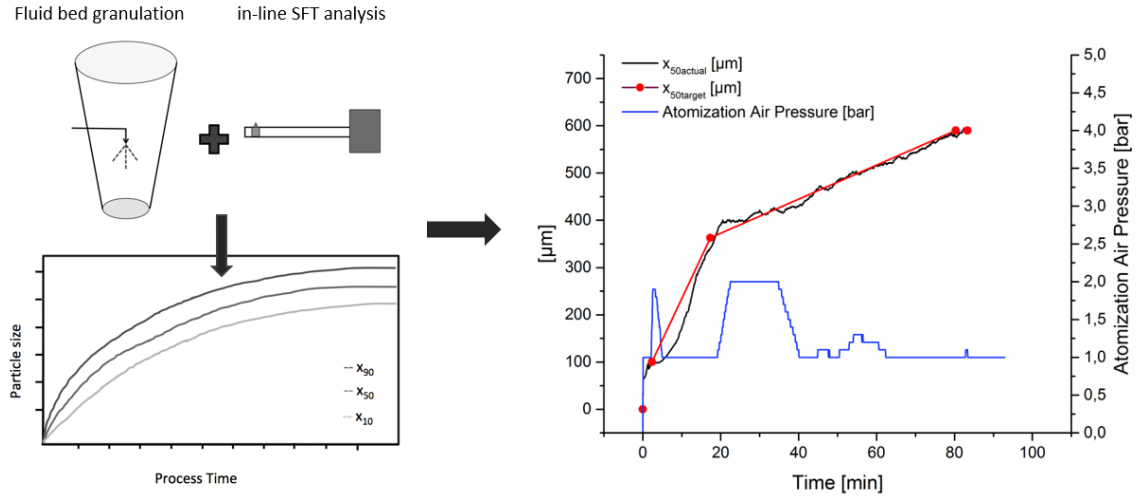

Figure 1. Schematic of experimental setup (left), experimental data including target curve, actual particle size data and response of process variable (right)

[1] L. Madarász *et al.*, "Real-time feedback control of twin-screw wet granulation based on image analysis," *Int. J. Pharm.*, 547 (1-2) (2018) 360-367.

84. APPLICATION OF MODELING TOOLS FOR RAPID EARLY PHARMACEUTICAL TABLET FORMULATION DEVELOPMENT

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Tablet development in the early phases of pharmaceutical development is challenging due to limitations in active pharmaceutical ingredient (API) availability, accelerated development times and changes in target dose. Designing a tablet formulation traditionally requires extensive trial-and-error experimentation to find mixtures of constituent powders that can meet the desired target quality attributes. A recent publication presents a new model for predicting the tensile strength of compressed pharmaceutical powder mixtures [1]. This model has been harnessed as part of a tool called 'Virtual Tablet Designer (VTD)'. VTD enables API to be mixed with various excipients to compensate for lack of former's tabletting properties and predict the compaction attributes of the final formulation manufactured by direct compression or roller compaction. In this approach, only a small quantity of API is required to characterise the compressibility and compactability properties. Several in-silico formulations were generated for an investigational API, and formulations that met the quality target profile were subjected to experimental work. Good correlations were found between the predicted and experimental values for formulations manufactured by roller compaction with varying drug load.

Another predictive tool 'Roller Compaction Calculation Tool (RCCT), based on modeling the pressure distribution in a roller compactor [2], was used for transferring the product between sites/equipment by predicting the key process parameters required to meet the tablet CQAs [2]. RCCT provided excellent goodness of fit for the studied formulations and thus aided in seamless transfer of product for GMP manufacture. Integration of computer modelling and material characterization enables a rapid, robust and API-sparing approach for formulation design, producing significant savings in resources and time without comprising the quality/performance of final product.

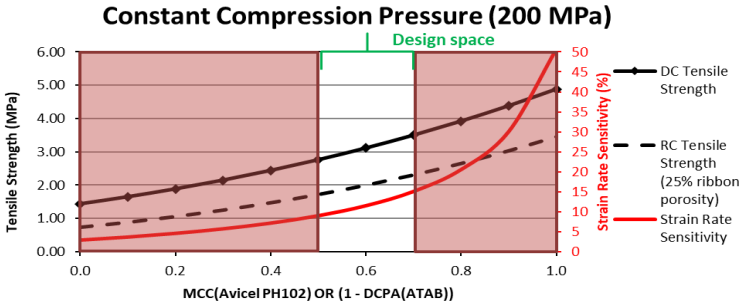

Figure 1. VTD plot with 20% API loading showing the predicted tensile strength and strain rate sensitivity

[1] G.K. Reynolds, J.I. Campbell, R.J. Roberts, A compressibility based model for predicting the tensile strength of directly compressed pharmaceutical powder mixtures, International Journal of Pharmaceutics, 531 (2017) 215-224.

[2] G.K. Reynolds, R. Ingale, R. Roberts, S. Kothari, B. Gururajan, Practical application of roller compaction process modeling, Computers & Chemical Engineering, 34 (2010) 1049-1057.

85. RECONSTITUTION OF FOOD POWDERS: RECENT PROGRESSES AND UPCOMING CHALLENGES

Jana Kammerhofer[1], Robert Mitchell[1], Julien Dupas[2], Alessandro Gianfrancesco[3] & Laurent Forny[1]

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Dehydrated beverages remain a major business opportunity with continuous growth in term of products launches and sales [1]. Hence, the *Science of Reconstitution* attracted major interest from both Academia and Industry over the past 20 years as illustrated by an almost constant increase of scientific publications and patents [2,3]. Thanks to this joint effort, some of the scientific gaps identified in 2009 were partially filled [4]. Among others, major progresses were made in understanding wetting, capillarity and dispersion of soluble surfaces. A summary of our most recent achievements will be provided [5-7].

Yet, challenges remain especially in view of new product innovations driven by major consumers trends such as organic or sugar reduction. These innovations are often calling for extended scientific understanding and tailored reconstitution performance. Several examples will be discussed highlighting upcoming challenges such as understanding reconstitution of functional ingredients (e.g. tastant, encapsulated bioactive) in complex products (e.g. fat based matrices) and in complex environment (e.g. mouth, digestive track); example of objective for the industry being able to link physical properties to sensory perception and bioavailability.

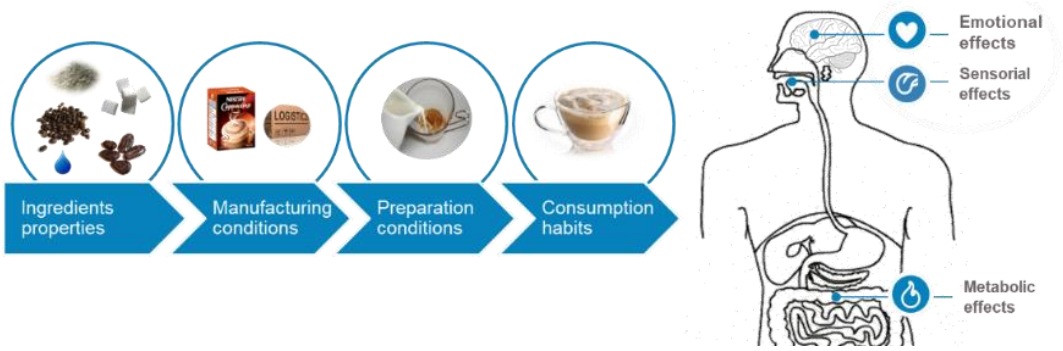

Figure 1. The numerous scientific challenges toward educated design of soluble products

[1-3] Euromonitor international, 2018 / Scopus, 2018 / Intellixir, 2018

[4] L. Forny, A. Marabi, S. Palzer, Wetting, disintegration and dissolution of agglomerated water soluble powders, Powder Technology. 206 (2011) 72–78.

[5] Kammerhofer, J., Fries, L., Dymala, T., Dupas, J., Forny, L., Heinrich, S., and Palzer, S. Penetration rates into heterogeneous model systems and soluble food material. Powder Technology, 339 (2018) 765-774.

[6] J.Dupas, V.Girard, L.Forny, Reconstitution Properties of Sucrose and Maltodextrins, Langmuir 33 (2017) 988–995.

[7] Mitchell, W.R. (2015) Mechanisms of food powder dispersion in a liquid medium. PhD thesis, University of Sheffield, UK

86. PREPARATION OF NANOPARTICLES VIA BUBBLE BURSTING

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When a bubble ruptures in the nature circumstance, it projects hundreds or millions of tiny droplets in the air. Across the oceans in the world, an estimated 1018 to 1020 bubbles burst every second [1] and form the sea spray aerosols, playing a crucial in the earth climate system. At a smaller range, the bubbles in a glass of soda rise towards the surface and burst, producing aerosols. Therefore, bubble bursting process is considered to be a promising way to give birth to micro- or nanosized particles.

In this study, the rupture behaviour of microbubbles generated in a microfluidic T-junction was applied to create nanoparticles. Before the rupture of the microbubbles, the size and state of the group were captured and analysed using high-speed microscopy and digital image technology. The rupture of the bubble was conducted by two methods, the free mode and the vacuum mode. The products of these two methods were examined by using a NOVA NanoSEM 450 scanning electron microscope and then were compared. It is found that the free mode produces smaller particles and the vacuum mode is more controllable. Additionally, the effect of the hydrophobicity of the rupture surface was investigated. The consequence shows the superiority of the hydrophobic surface. Finally, the influence of liquid viscosity and bubble diameter on the particle size was carried out. The particle size decreases with the liquid viscosity and increases with the bubble diameter.

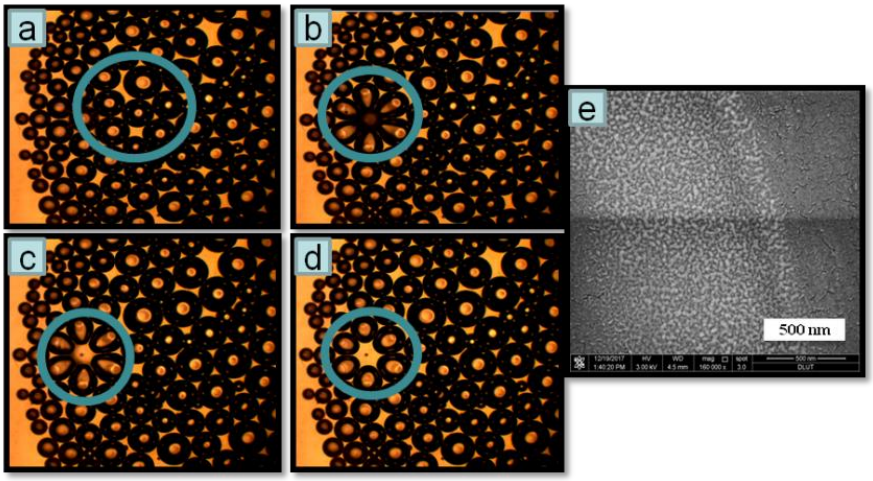

Figure 1. Microbubbles bursting process (a–d) and the nanoparticles obtained (e)

[1] T. Séon, G. Liger-Belair, Effervescence in champagne and sparkling wines: From bubble bursting to droplet evaporation, The European Physical Journal Special Topics, 226 (2017) 117–156.

87. ADHESION FORCE MEASUREMENT BY CENTRIFUGE TECHNIQUE AS A TOOL FOR PREDICTING INTERACTIVE MIXTURE STABILITY

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Recently, many modern active pharmaceutical ingredients (APIs) exhibit poor water-solubility, causing difficulties in the development of solid dosage forms with sufficient bioavaiability. While it is given that as surface area in contact with liquid increases, the dissolution rate increases, increasing the surface area by particle size reduction does not always exhibit an improvement in dissolution rate. It is due to tendency for micronized substance to form aggregates or clusters in the solvent so that the effective wetted surface is reduced again. Therefore, fixing the API on the surface of larger excipient particles by forming the interactive mixture helps to overcome this problem and to enable large surface area being available for the dissolution. The stability of an interactive mixture is determined by relative magnitude of both cohesive forces between fine API particles and adhesive forces between API particles and coarse carrier particles. Adhesion forces should exceed cohesive ones in order to obtain uniform and stable interactive mixtures. Therefore, the aim of this study was to verify the adhesion force measurement as a tool for predicting interactive mixture stability.

Unlike the atomic force microscopy, which can only determine the adhesion of a single particle per experiment, the centrifugal technique is able to measure adhesion force distribution of a large number of particles. This technique is based on the detachment of particles from a surface due to centrifugal force. Therefore, experiments were carried out by repeated exposure of a system of deposited particles on a carrier surface by centrifugation, at a progressively increasing rotation speed, and thus by the increasing centrifugal force acting on the particles. In the pilot phase of this work, excipient particles were chosen as model substances, both for the preparation of the carrier surface and deposited particles. An optical microscope with NIS-elements software (Nikon Inc., Japan) was used to quantify the number of particles retained on the carrier surface after each centrifugation step. Adhesion forces were then assessed by a newly proposed criterion, apparent adhesion strength $Y_{A.}$ As expected the developed methodology for measuring the adhesion force by centrifugation method in combination with optical microscopy could demonstrate how surface texture affects adhesive interactions. Results showed that the key factor influencing adhesion in system deposited particle - carrier surface could be the real contact area. It seemed that the larger the real contact surface, the stronger the interaction created in this system and thus greater forces would be required to detach particles from the carrier surface.

Despite results above, using the optical microscope to quantify the number of particles is extremely sensitive to properties of deposited particles on the measured surface as well as the position of light source. Therefore, the experimental technique is in the process of ongoing development to improve the way, how to obtain more accurate results. Moreover, in the next phase of study, API will be used as a model substance in the system studied.

88. COATING OF FINE-DISPERSE PARTICLES IN FLUDIZED BED

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In coating and granulation processes, a suspension or solution is sprayed on the carrier particles and the liquid film is created on the surface of every single particle. By evaporation of the liquid new solid layers are formed, which results in an onion-like growth of the particles. Regarding these particle formation processes, several process technologies are available, for example, the mixers and fluidized beds installed with a spray nozzle. Normally, for these apparatuses, the size of the processing particle can range from approximately 100 µm up to several centimetres. For fine-disperse particles, which are smaller than 60µm, the use of these technologies gets increasingly difficult due to the onset of the cohesive behaviour of the particles. The reason for this is that the microscopic attractive forces between the particles increase with decreasing particle size. The smaller the particles the more they are likely to cause the formation of agglomerates: lumping of two or more individual particles into one larger structure. If such a composition is coated and breaks up afterward, defects in the coating layer develop which may significantly reduce product quality.

This work contributes to the development of a coating process of fine dispersed particles by combining the fluidized bed with a fog generator. The feasibility of the operation is based on and demonstrated by the application of the fog generator. The coating solution will be firstly atomized by compressed air through the fog generator. Thereafter the further coating process is conducted through the contact between the fog droplet (diameter less than 10µm) and the small particle in a fluidized bed. Due to the relative size relationship between small droplets and particles, smaller droplets can significantly reduce the chance of agglomeration during the coating process. In this way, the improvement in coating uniformity is noticeable, and the quality of fine disperse particle coating-products can be guaranteed.

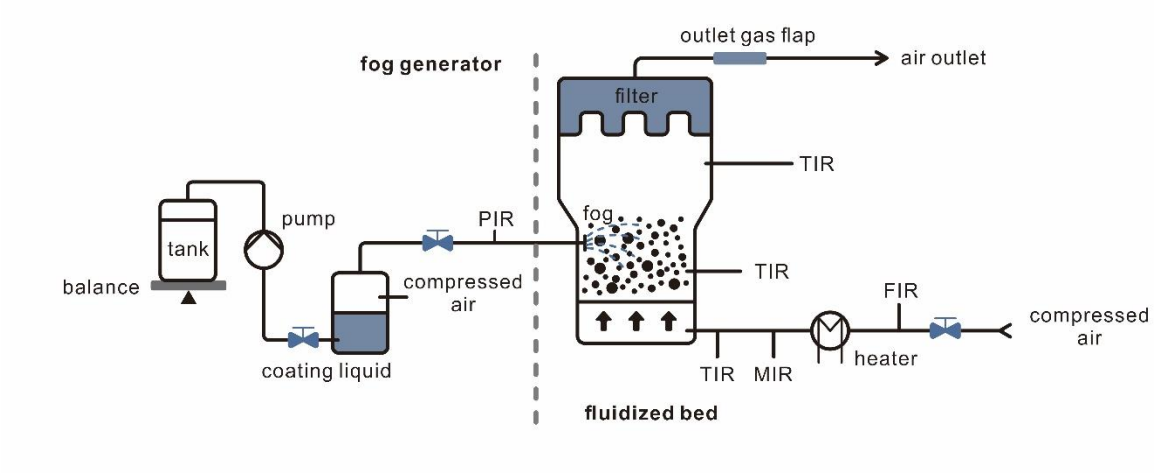

Figure 1. Scheme of the fluidized bed and fog generator.

89. QUANTIFYING FLOWING PROPERTIES OF SPRAY-DRIED POWDERS BEFORE AND AFTER GRANULATION

Geoffroy Lumay[1], Liselotte De Smet[2], Filip Van der Gucht[3], Filip Francqui[4] & Naveen Mani Tripathi[4]

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2 Xedev, Zelzate, Belgium
3 ProCepT, Zelzate, Belgium
4 GranuTools, Awans, Belgium
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We study the flowing properties and the density of spray-dried powders produced with different nozzles and different airflow rates. The obtained grains are small and have a low flowability. Therefore, an extra-streaming process is necessary before tableting. The spray-dried grains have been granulated with both High shear granulation (HSG) process and Fluid bed top spray granulation (FBG) process. The obtained granules have a lower cohesiveness than the spray-dried powder. We show how the different flow measurements (improved angle of repose from GranuHeap instrument, cohesiveness from GranuDrum instrument and improved Hausner ratio from GranuPak instrument [1,2]) can be analysed to draw conclusion about the process-ability in a tableting process. Finally, we show how these results are correlated with grain sizes/shapes distributions.

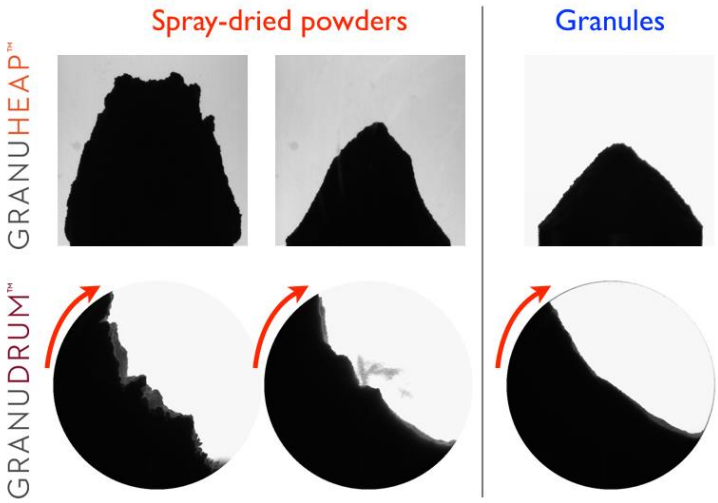

Figure 1. Typical pictures of heaps (GranuHeap) and of the flow inside the rotating drum (GranuDrum) with two spray-dried powders and with granules.

[1] F. Boschini, V. Delaval, K. Traina, N. Vandewalle, and G. Lumay, Linking flowability and granulometry of lactose powders, Int. J. of Pharmaceutics, 494 (2015) 312-320.

[2] G. Lumay, F. Boschini, K. Traina, S. Bontempi, J.-C. Remy, R. Cloots, and N. Vandewalle, Measuring the flowing properties of powders and grains, Powder Technology, 224 (2012) 19-27.

90. ULTRATHIN COATING OF PARTICLES IN FLUIDIZED BED USING SUBMICRON DROPLETS

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Spray coating of fluidized particles is a widely used industrial process. To produce sprays, nozzles of different design can be utilized. In commercial setups, nozzles produce polydisperse sprays with droplet sizes typically distributed between 10 and 100 μm, and mean droplet diameters of the sprays are usually ~50 μm. This allows obtaining coating on particles of 0.5-1 mm in diameter, but the thickness of such coating is usually several tens of microns.

In this work, we demonstrate a novel particle coating system, which, instead of traditional spray, uses ultra-fine droplet aerosol to produce substantially thinner than usual coating on particles in a fluidized bed. In our experimental studies, 30 wt.% sodium benzoate-water solution was atomized by recently developed microspray atomizer [1] into very small droplets with Sauter mean diameter of D[3,2]=0.7 μm (measured by laser diffraction, Malvern Spraytec). The generated droplet aerosol was supplied into the chamber of laboratory-scale fluidized bed (Glatt GPCG 1.1) from the one side. Two types of particles were coated, inorganic γ-Al_2O_3 and organic cellulose pellets (cellets), both having mean diameter ~600 μm. The results demonstrated that submicron droplets enabled particle coating with simultaneous drying at modest temperatures of fluidization air of 30-60 °C. After 1 hour of continuous operation of the setup, the coating thickness on the particles was as small as ~2.7 μm (measured by a scanning electronic microscopy) and the process yield was ~30%, improvable with recycle.

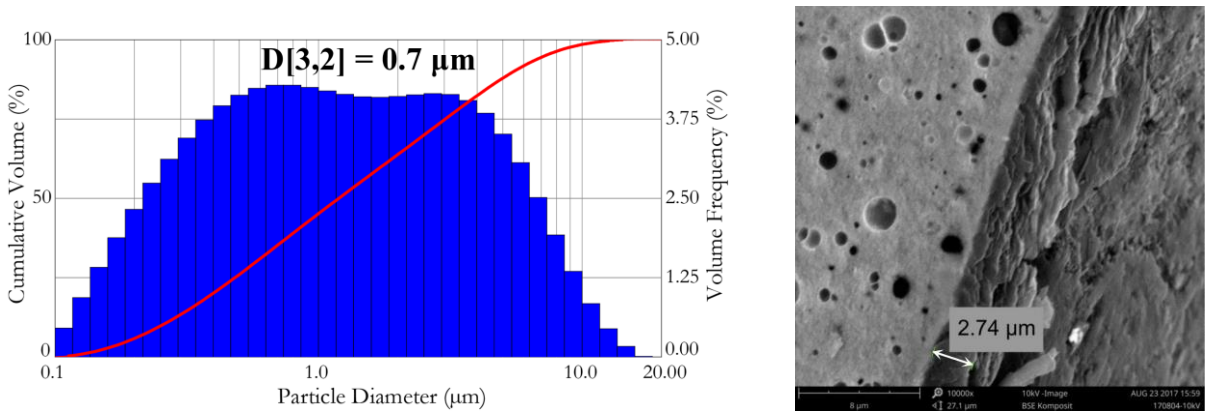

Figure 1. Size distribution of generated droplets (left) and thickness of coating on dry particle (right)

[1] M. Mezhericher, J.K. Nunes, J.J. Guzowski, H.A. Stone, Aerosol-assisted synthesis of submicron particles at room temperature using ultra-fine liquid atomization, Chemical Engineering Journal, 346 (2018) 606-620.

91. RELATING PHYSICAL CHARACTERISTICS OF FOOD PARTICLES TO DYNAMIC FLOW BEHAVIOUR

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The vast majority of products in the food industry require the proper handling of ingredients, intermediary products and final products in powdered form. To obtain a stable process, the mastery of powder flowability is essential for ensuring proper dosing, dry-mixing homogeneity, silo discharge and other various processes [1, 2]. Often in food innovation and renovation, a powdered food ingredient needs to be modified or replaced, which can lead to unpredictable and expensive complications related to powder flow. Too often, the specifications given to suppliers are vague and unactionable with regards to flowability. To reduce the costs of qualifying new ingredients, there is a need to be able to effectively describe their behaviour under a given processing step and to make meaningful predictions based on their physical properties.

The challenge comes from the complexity of the flowability concept, the mechanisms behind which differ according to the process [3]. Shear cell measurements are widely used to assess the flowability for applications that involve powder discharge; in the scope of processes with lower stresses such as screw feeding or dry mixing, newer lower-stress dynamic flowability measurements are now available using powder rheometers (such as Freeman Technology FT4). However, unlike the rheometry of liquids, the powder rheometry results are not evident at first glance and can often be misinterpreted. To understand better the meaning of these measurements and their relevance to our processes, we highlight the value of visual assessment of powder texture and flowability.

The objective of the present work is therefore to link flowability measurements of powder rheometer with visual dynamic flow behaviour to determine the most relevant parameters, while screening powders for their physical properties (size and shape) to make meaningful predictions for low-stress processes. Two representative examples of rheometry measurements are presented.

The selected parameter allowed us to find meaningful correlations with the physical properties (size and shape) of the powders and to compare the production processes of food powders from a flowability point of view.

[1] Harnby, N., Edwards, M.F., Nienow, A. W. Mixing in the Process Industries: Second Edition. Butterworth-Heinemann, 1997

[2] Leturia, M., Benali, M., Lagarde, S., Ronga, I., Saleh, K. Characterization of flow properties of cohesive powders: A comparative study of traditional and new testing methods. Powder Technology, Vol. 253, pp. 406-423, 2014.

[3] Freeman, R. The characterisation of powder and bulk material – a multivariate approach using dynamic, shear and bulk property measurements. Bulk Solids India, April 6th to 8th, 2011.

92. MODELLING THE CAPILLARY FORCE BETWEEN PARTICLES WITH UNEQUAL CONTACT ANGLE

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As two particles with a thin liquid film collide with each other, the liquid films merge to form a pendular liquid bridge, which can introduce a strong capillary force between the two particles. The capillary force is decided not only by the particle size but also the contact parameters, such as liquid volume, contact angles of liquid on each substrate, half-filling angle to each particle as well as the separation distance [1].

Considering all of these impact factors, a more general capillary force model was established in this study using the software of Surface Evolver. The validity of the model was confirmed by comparing results to those obtained through analytical expressions and a recently developed closed-form equation. This newly developed capillary force model can be used to calculate the capillary force between any two adhesive particles with different diameter and contact angles in a polydisperse particle system.

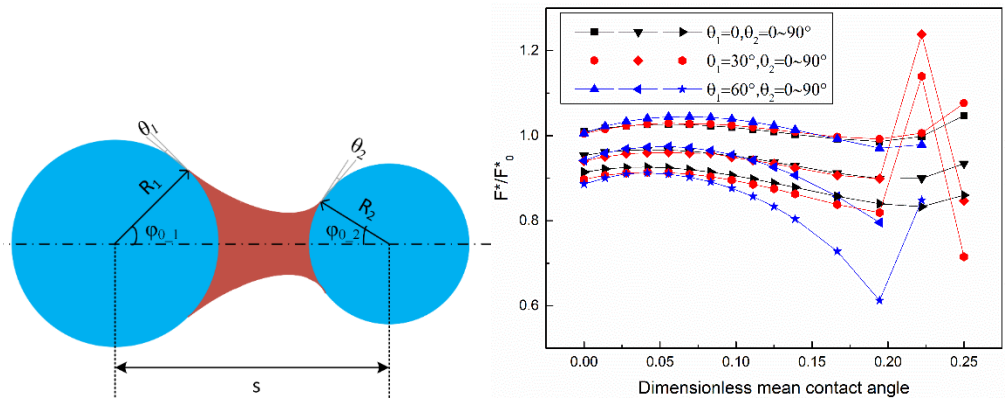

Figure 1. Capillary force between two unequal particles with unequal contact angle

[1] J.S. Marshall, S. Li, Adhesive particle flow: a discrete-element approach: Cambridge University Press, Cambridge, 2014.

93. EFFECT OF GRANULATION ADDITIVES ON THE HARDNESS AND SURFACE ABRASION OF FERTILIZER GRANULES

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Fertiliser developments are providing important improvements in plant nutrition, crop yields, environmental safety and human health. The efficacy of fertilizers depends on both the granule chemistry and the lesser acknowledged but equally important physical characteristics. Improvements in physical quality of granules are needed given these products are being moved by heavy mechanical equipment, shipped around the world and stored for long periods under different climatic conditions.

Granule hardness is one important factor that if low, can result in higher dust loadings and poor abrasion resistance leading to high moisture uptake in highly humid conditions, all of which can result in handling difficulties and uneven soil application. In this work, the physical attributes of fertilizer granules produced in a laboratory coating drum were assessed using a range of granulation additives to assist with granule binding and hardness. These necessarily have to be non-hazardous and ideally inexpensive. The products were examined and assessed for granule hardness and degradation due to surface abrasion under a range of simulated storage conditions.

Figure 1. Monoammonium phosphate with ZnO

94. EFFECT OF SURFACTANT VARIATIONS ON THE PENETRATION TIME OF HYDROPHILIC MICRON PARTICLE IMPACTING INTO THE GAS-LIQUID INTERFACE

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Micron particle impaction behavior plays an important role in the performance of wet scrubbing and many applications of industry. The investigation of particle penetration time during the submergence process will contribute to searching the method of strengthening the particle collection efficiency. In the current work, the effect of surface tension (44.3mN/m ≤ γ ≤ 73.9mN/m) on the penetration time has been investigated under different concentrations of ethanol, anionic surfactant (SDBS), nonionic surfactant (AFS) solutions. The penetration time will all exhibit a power function to the particle size at lower impact velocity (up0 ≤ 0.5m/s), which increase with the increased concentration of ethanol, while decrease with the increased concentration of anionic and nonionic surfactants. Besides, the width of interfacial deformation will gradually expand for surfactant solutions and may be confined for ethanol solutions. It is proposed that Marangoni effect will be induced when the solute (ethanol) contained in the water is volatilizing during the penetration process and cause the surface tension gradient. The interface will be confined and unexpectedly enhance the capillary force exerted on the particle, further extending the penetration time. Otherwise, the penetration time will be shortened with the increased concentration of surfactants since the wetting rate of liquid on the particle surface is improved with the decrease of surface tension.

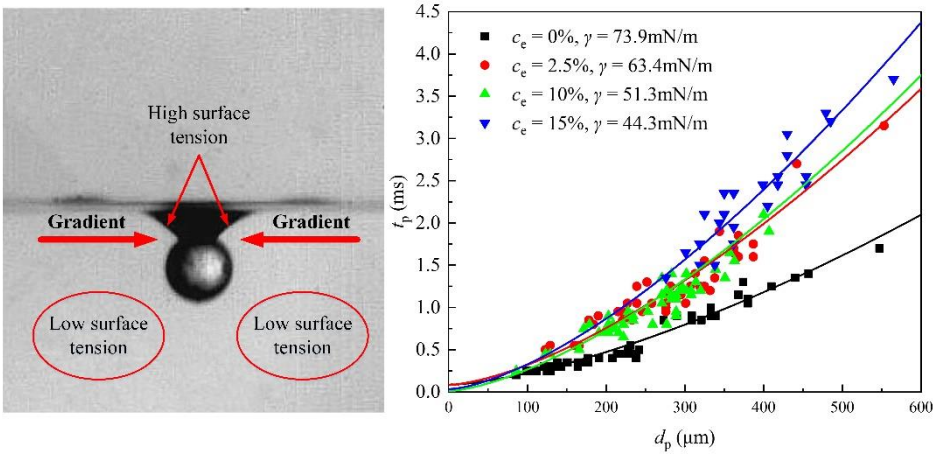

Figure 1. Micron particle penetration process in the ethanol solution

95. GROWTH CHARACTERISTICS OF FINE PARTICLES WITH DIFFERENT WETTABILITY DURING VAPOR HETEROGENEOUS CONDENSATION

XueLi Chen [1,2], RunZhe LIU [1,2], ShiJie ZHU [1,2], Xin ZHONG [1,2], DeXi MENG [1,2] & HaiFeng LU[1,2]

1 Key Laboratory of Coal Gasification and Energy Chemical Engineering of Ministry of Education, East China University of Science and Technology, Shanghai 200237, China
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In this paper, the effects of supersaturation (1.1 ≤ S ≤ 1.8), residence time (0.6s ≤ t ≤ 2s), initial number concentration (1.35×106A/cm3 ≤ c ≤ 2.7×106A/cm3) and initial particle size distribution (3.5μm ≤ dp ≤ 5.1μm) on the growth characteristics of different wettability fine particles have been investigated by using modified spherical glass beads. The growth rate was used to characterize the growth of fine particles. The results show that the growth rate of fine particles will increase with the increase of supersaturation and residence time under the similar particle size distribution and particle wettability. The growth effect will perform better for the particles with better wetting performance. Besides, the smaller the initial particle size is, the better the particle growth will be. The increase of initial particle concentration is not conducive to condensation of vapor on fine particles. When the supersaturation is 1.49, the residence time is 1s, initial number concentration is 1.35×106A/cm3, and initial particle size distribution is 3.85μm the growth of hydrophilic particles is the best and the growth rate can reach 144%.

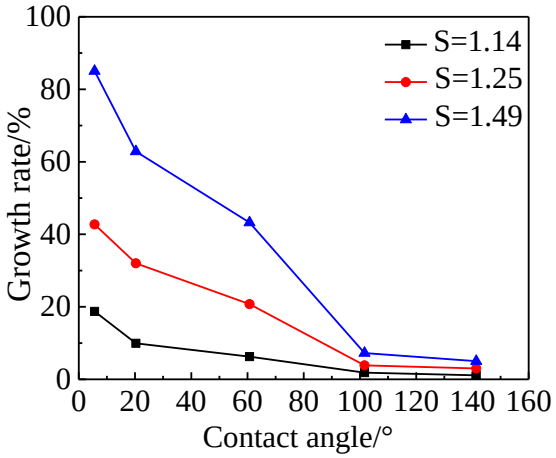

Figure 1. Effect of supersaturation on the growth of different wettability fine particles

96. DOUBLE EMULSION (W/O/W) BASED PCL MICROPARTICLES TO ENCAPSULATE MICROBIAL CELLS

Fengxia Liu, Chao Dong, Wei Wei, Zhiyi Li, Chunyu Wang, Jinyu Zhao & Zhijun Liu

R&D Institute of Fluid and Powder Engineering, Dalian University of Technology, Dalian 116024, China
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The efficiency of double emulsion based microencapsulation for the encapsulation of microbial cells was investigated. Two-step emulsification method was adopted to prepare the yeast cells encapsulated double emulsions. Here instead of using one organic solvent as oil phase, a mixture of dichloromethane (DCM) and ethyl acetate (EA) was employed to match the density of water. The influences of various process parameters on the size of oil globules/PCL particles and encapsulation efficiency of yeast cells were investigated. As the size of oil globules altered, the type of double emulsion also changed, which led to an important difference in encapsulation efficiency. The results showed that both the size of oil globules/PCL particles and encapsulation efficiency: 1) decreased significantly with the increase of the stirring speed; 2) decreased with a proloned stirring time; 3) increased first and then decreased with the increase of the PVA concentration; 4) decreased as the amount of Span 80 added into the primary increased and 5) increased as the amount of PCL dissolved in the oil phase increased. Additionally, it was found that using the mixture of EA and DCM could significantly enhance the quality of the double emulsion.

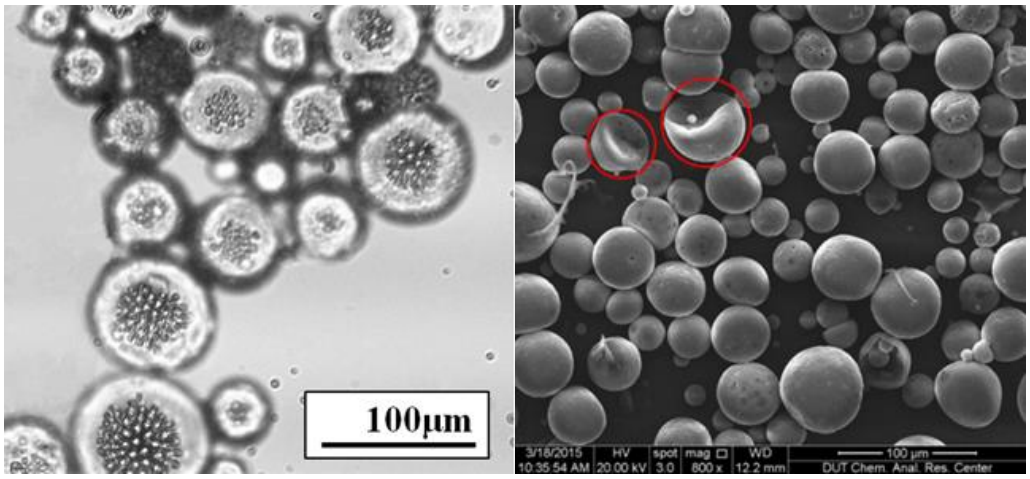

Figure 1. Optical microscopic and SEM images of the yeast cells laden microparticles prepared by double emulsion diffusion method.

97. HYDRODYNAMIC SIMULATION OF MOVING BED HEAT EXCHANGER

Zhijun Liu, Fengxia Liu, Xiaofei Xu, Chaoyang Wang & Wei Wei

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Moving bed heat exchanger with waved plates as heat transfer element, as a kind of spacing heat exchanger, is suitable for granular cooling, and we call it as Wave-Plate Heat Exchanger (WPHE), too. For granule heat exchange, the energy transfers from the granule to adjacent granules/wall. So the motion of the particles and the flow pattern of granules is necessary to be studied.

In this work, the hydrodynamic performance of 2-6mm Polyethylene in a moving bed exchanger was simulated using Discrete Element Method (DEM). The hydrodynamic characteristics, such as flow pattern, distribution of stress, velocity and trajectory of particles, and the effluence of the waved plate spacing (25mm, 30mm, and 38mm) were analysed in the process of granular flow. The results indicated that the transient stress between waved plates was heterogeneous; the zigzag-like pressure profiles on the waved pate increased. The motion trajectory of the granules in the direction of the vertical plate was influenced by the plate profile, that is to say, the vertical motion dominate the mixture. As the granules speed up, the number of granules contacted with the plate decreases, whereas the normal contact force changes little and is independent of the plate profile in the scope of this study. Conclusions could be drawn that the formation of dense particle clusters disturbed spatial homogeneity and resulted in collisional anisotropy which was propitious to enhance the process of momentum, heat and mass transmission.

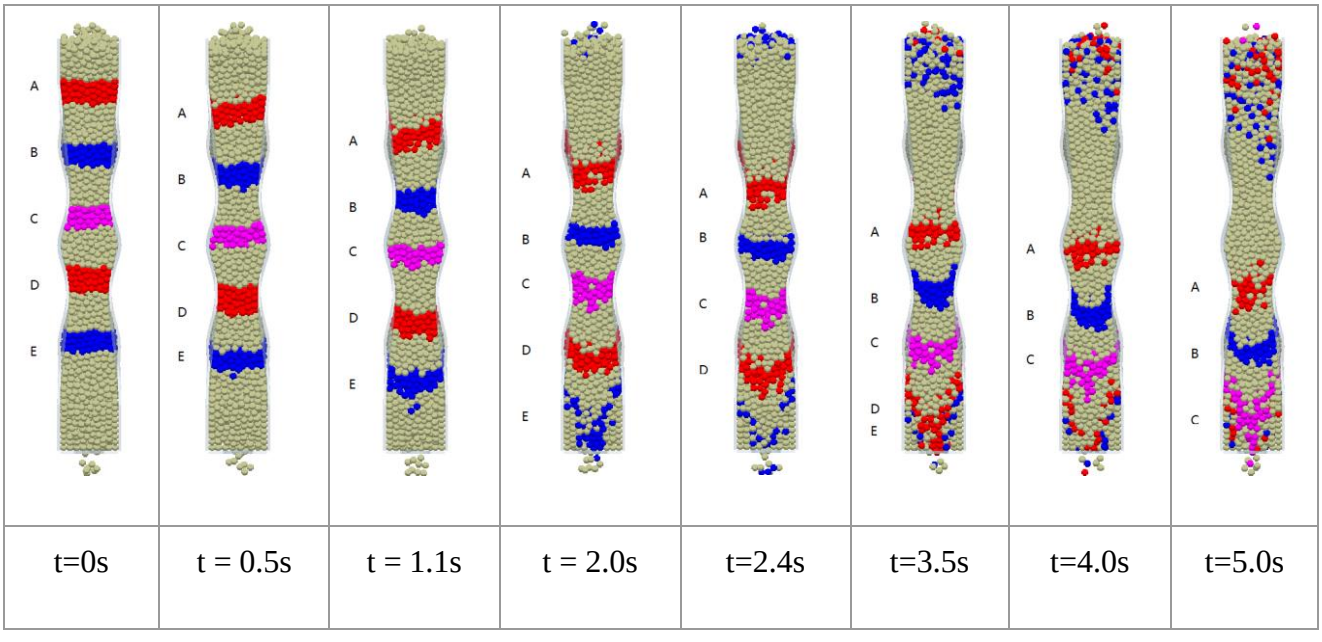

Figure 1. Flow pattern inside wave plate flow channel

98. INFLUENCE OF COMPRESSION CONDITIONS ON THE COMPACTIBILITY OF THERMALLY PROCESSED POLYMERS

Ioannis Partheniadis[1], Miltiadis Toskas[1], Alexandros E. Karantzalis[2] Nizar Al-Zoubi[3] & Ioannis Nikolakakis[1]

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2 Dept of Materials Science & Engineering, University of Ioannina, 45110, Ioannina, Greece
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Hot melt extrusion (HME) is increasingly applied in the pharmaceutical industry for the formulation of solid dispersions of drugs aiming at solubility improvement and modulation of drug release characteristics [1]. The processing of extruded pellets into powders by milling and subsequent compression into tablets raises the issue of tabletability due to the adverse effect of the therno-mechanical HME treatment on the elasto-plasticity of powdered extrudate.

In this work the compaction of HME polymeric powders commonly employed in pharmaceutical manufacturing was investigated at different punch speed and homologous temperature (Th = Compression temp./Tg) using polymers of different chemistry and function in pharmaceutical formulations. Polymeric powders were characterized before and after HME for thermal properties, indentation microhardness and compaction behavior, by fitting established and newer compression models into compression pressure – porosity data. The work of compaction, elastic recovery and ejectability were also obtained from 'in-die' measurements and mechanical strength by diametric loading, and were compared between the HME and unprocessed polymers. It was found that compression conditions greatly affected the compaction process and tablet quality. For certain compression speed/Th combinations, the improvement for the tablets from powdered extrudate was such that there was no noticeable difference with the corresponding tablets of unprocessed powder.

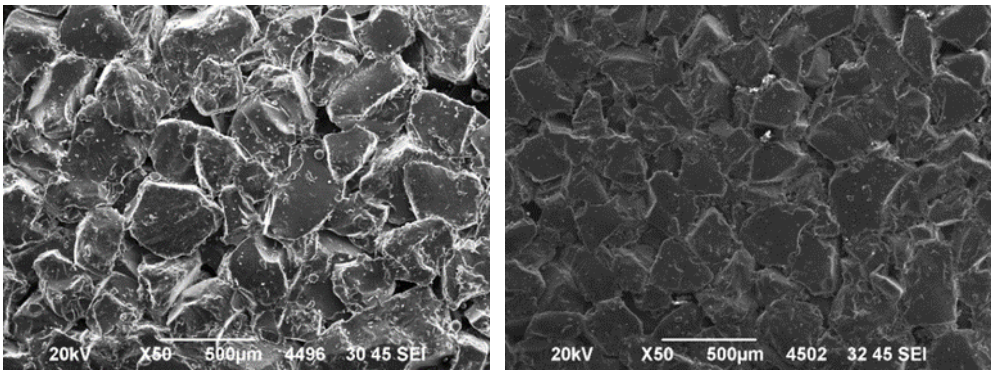

Figure 1. Kollidon SR powdered extrudate compressed at Th=0.5 (left) and Th=1.0 (right)

[1] T. Avgerinos et al., Mechanical properties and drug release of venlafaxine HCl solid mini matrices prepared by hot-melt extrusion and hot or ambient compression, Drug Development and Industrial Pharmacy 44(2) (2018) 338-348.

99. COMPARISON OF THE MECHANICAL PROPERTIES OF HYDROPHOBIC STARCH ESTERS

Nizar Al-Zoubi[1], Adel Ardakani[2], Faten Odeh[2], Nina Sakhnini[2], Ioannis Partheniadis[3] & Ioannis Nikolakakis[3]

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Hydrophobic starch esters have demonstrated high potential as matrix formers in controlled-release drug delivery systems [1]. In continuation of their evaluation, the mechanical properties and tableting performance of native starch, starch acetate and starch propionate were compared.

Particle microhardness and modulus of elasticity were measured by nanoindentation, and work of compaction, elastic recovery and ejectability from 'in-die' measurements of compacted powder. Compaction data were analyzed using established and newer compression models. For all starches, yield pressure clearly increased with microhardness. Between the two esters, starch propionate showed lower microhardness, lower yield pressure and better ejectability. Its mechanical strength was lower that the acetate, but still adequate (~2 MPa) to form good tablets. Principal component analysis was able to organize the studied properties (variables) by reduction of the data to three components explaining 96.5% of the total variance. Examination of the components assisted in the derivation of relationships between the studied mechanical properties and tablet strength.

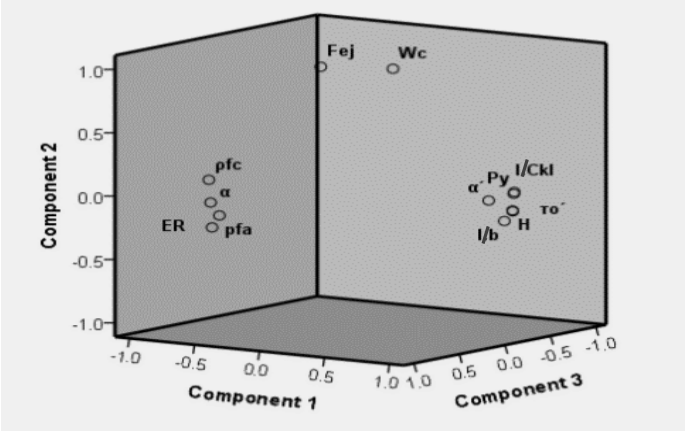

Figure 1. Component plot from PCA analysis showings variables organized in space.

[1] N. Sakhnini, N. Al-Zoubi, G.H. Al-Obaidi & A. Ardakani, Sustained release matrix tablets prepared from cospray dried mixtures with starch hydrophobic esters. Die Pharmazie 70 (2015) 177-182.

100. OPTIMIZING THE OPERATIING PARAMETERS FOR PHARMACEUTICAL FLUDIIZED BED DRYER BY PROCESSS TOMOGRPAHY AND CFD MODELING

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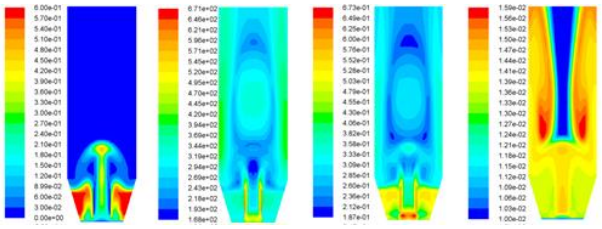
1 Institute of Engineering Thermophysics, Chinese Academy of Sciences, Beijing 100190, China
2 University of Chinese Academy of Sciences, Beijing 100049, China
3 School of Electrical and Electronic Engineering, University of Manchester, Manchester, M13 9PL, UK
E-mail: wanghaigang@iet.cn

Fluidized beds are typical used in pharmaceutical industry for pellets drying, coating and granulation. The operation parameters, i.e. inlet air temperature, inlet air relative humidity and velocity affect the mass and heat transfer between the gas phase and particles which also affect the end-point product quality [1]. Therefore, it is important to properly optimize and control the fluidized bed process based on advanced on-line process analytical tool (PAT). In this research, process tomography as a non-intrusive and non-invasive PAT tool will be used in the pharmaceutical fluidized bed drying process. Meanwhile, CFD model based on two-phase fluid model coupled with heat and mass transfer will be used to model the heat and mass transfer phenomena in the drying process and used to validate the measurement results. The CFD simulation is applied in two types of fluidized bed dryers, i.e. conical shape fluidized bed and conical shape fluidized bed with Wurster tube. The gas-solids flow hydrodynamic characteristics, heat and mass transfer performances in the two types of dryer were comparatively studied based on the CFD simulation and ECT measurement. Key drying process parameters including solids moisture content, solids concentration and temperature, are investigated and the effect of operating parameters are addressed both based on the measurement and simulation. The results give invaluable information for the performance of fluidized bed drying process.

Fluidized bedwith Wurster tube



Fluidized bed

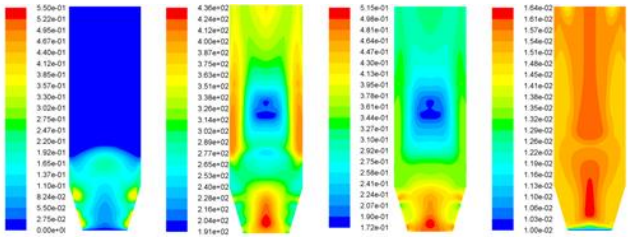


Figure 1. CFD simulation for solids concentration, mass nad heat transfer coefficient

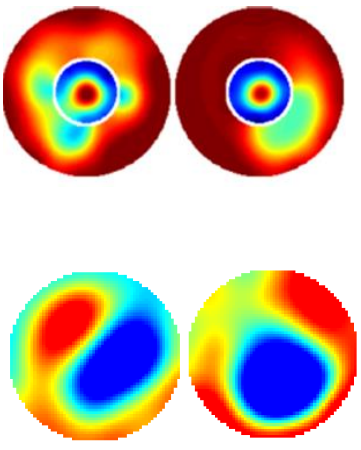


Figure 2. ECT image reconstruction for solids distribution

[1] H.G. Wang, W.Q. Yang, P. Senior, R.S. Raghavan and R.S. Duncan, Investigation of batch fluidised bed drying by mathematical modelling, CFD simulation and ECT measurement, AIChE J., 54 (2008) 427-444.

101. HIGH TEMPERATURE FLUIDIZED BED SPRAY COATING - NEW POSSIBILITIES IN CATALYST DESIGN

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Particle coating processes have the purpose of functionalizing powder or granular solids. The goal of these processes is to improve product performance by changing physical and chemical particle properties, adding surface activity to carrier particles for e.g. heterogeneous catalysis or adsorption. Depending on the material, area of application and target parameters to be defined, various methods and different techniques can be selected. Typically, fluidized bed spray coating processes take place at temperatures well below 200 °C, which is in most cases entirely sufficient for the coating and functionalization of particles. However, in special cases an additional thermal treatment is necessary to achieve the specified product or product properties, e.g. an additional calcination, reduction, oxidation or a phase transformation. This requirement applies increasingly with complex catalyst materials and conventionally is realized by subsequent costly process steps. For example, catalyst carriers are coated with a metal salt (e.g. metal nitrate) from an aqueous solution or dispersion. Subsequently the metal salt is calcined to form the desired metal or mixed metal oxide. A combination of coating and high temperature thermal treatment in only one process step has not been available so far and limited the application of the usual techniques for coating.

Glatt Ingenieurtechnik GmbH has developed a very flexible high temperature fluidized bed system up to 700 °C with simultaneous injection of liquids. The process temperature can be adjusted between 50°C and 700 °C, if required gradually in different temperature steps. So a particle coating and a chemical reaction may be done simultaneously or in sequence, as required. The concepts behind the powerful technology will be presented as well as exemplary use cases. Based on a concrete example, it will show the novel processes flexibility. The influence of different process and formulation parameters on coating mechanisms, yield and material properties will be shown for the application of mixed metal oxide catalysts coated carriers.

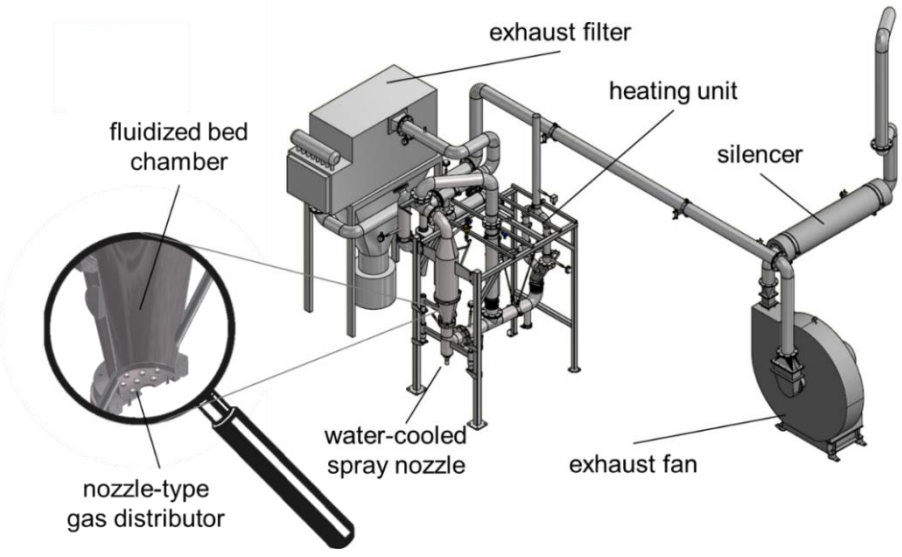

Figure 1. Set-up of high temperature fluidized bed spray coating system.

102. IMPACT OF COMPRESSION PRESSURE ON PHARMACEUTICAL FORMULATIONS CONTAINING MAGNESIUM ALUMINOMETASILICATES

Pavlína Komínová, Diem Trang Tran & Petr Zámostný

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Magnesium aluminometasilicates (MAS) belong to the synthetic materials having versatile utilization in pharmaceutical formulations. The Neusilin® series of commercially available products belong to the most frequent representatives. Neusilin® is an amorphous form of MAS available in various grades with different psychochemical properties. This makes Neusilin® convenient for applications in both direct compression and wet granulation in many roles.

Our previous research focused on using Neusilin® as a glidant revealed that the MAS ability to enhance flow properties of powder mixtures is largely based on repulsive character of its particle interactions, which is reported as "negative cohesion" by some authors. It was therefore assumed that this repulsive behaviour would likely affect the mechanical properties of tablets prepared from tested mixtures, such as decreasing tensile strength thereof. Our experimental results confirmed this assumption, but the effect was much less significant than anticipated. In addition, pure Neusilin® samples produced very strong tablets. This contrast indicated the Neusilin® ability to form strong bonds between particles at certain pressure threshold.

Therefore, the present work is aimed at investigation of mixtures comprising Neusilin® behaviour during their exposure to different pressures. The same blends prepared for basic research containing microcrystalline cellulose as model excipient and Neusilin® US2 and S2 grades as MAS representatives were included in this study. Cohesion force measurements at low pressures were performed using FT 4 powder rheometer (Freeman Inc., UK) via shear testing. Effective angle of internal friction served as the main parameter for determining the particle interactions in the bulk solid. GTP-1 compaction analyser (Gamlen Tabletting, UK) was used for preparing compacts at higher pressures and measuring the compaction parameters. Tablet strength measured using Multitest (Sotax, CH) was used as a measure of particle interactions. The main goal was to establish the threshold pressure at which bond creation exceeds repulsive character and at which pressed part (tablet) would form. The mixtures/tablets were also observed using SEM/BSE/EDS to monitor MAS particle interactions and facilitate understanding the processes responsible for the strong bond formation.

The results revealed that applied pressure had a thresholding effect on behaviour and character of Neusilin® containing mixtures. Tendency of Neusilin® particles to form bonds between one another and with particles of second excipient intensified with increasing pressure. Taken SEM pictures showed that spherical particles of Neusilin® were subjected to destruction which led to the formation of new surfaces and physical property changes. In conclusion, the study compared properties of microcrystalline cellulose blends containing the tested MAS in relation to the applied pressures. It was found that the pressure influences behaviour of MAS in a threshold pattern. The repulsive character prevails at low pressures and MAS particles act as a glidant. However, a bonding ability is emphasized when certain pressure is reached, and then they act as a binder. This "function switching" makes the MAS materials suitable for using as a multifunctional excipient in direct tablet compression.

103. INFLUENCE OF TYPE OF GRANULATORS ON FORMATION OF SEEDED GRANULES

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Seeded granulation occurs when small particles form around a larger core particle [1]. The large central particle becomes wetted and acts as a nucleus. The nucleus then gets covered in fine particles to form the seeded granule. Seeded granulation is used to increase the uniformity of the granule structure. This has applications in the pharmaceutical industry as it allows for even drug distribution through the granules as a seeded granule should be covered in one full layer of the fine particles. Seeded granulation also reduces dust in the product allowing for a more attractive product and efficient drug manufacture [2].

In this paper, calcium carbonate powder (Durcal 65) was used with a polyethylene glycol (PEG 4000) agglomerate in a Pharmalab 16 twin extruder. Two granulation processes were investigated, hot melt granulation and wet granulation. In hot melt granulation the PEG binder entered the extruder as a solid and was melted during the process. For wet granulation the PEG was in a 65% wt. aqueous solution. The seeded granules produced by hot melt granulation underwent characterisation testing to find the size and strength distribution. The internal structure was also examined. These results were compared with granules obtained by a Cyclomix batch granulator. It was found that particles produced in hot melt granulation are irregular. The mean size and strength of hot melt granulation produced less seeded structure as compared to the bath granulator. A further research is ongoing to discover effect of material properties on formation of seeded granules.

[1] Rahmanian, N., Ghadiri, M., and Jia, X. Seeded granulation. Powder Technology, 206 (2011) 53-62.

[2] Shanmugam S. Granulation techniques and technologies: recent progresses. BioImpacts : BI. 5 (1) (2015) 55-63

104. CONTINUOUS DETERMINATION OF GRANULE SIZE DISTRIBUTION USING DYNAMIC IMAGE ANALYSIS

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Roll compaction/dry granulation (RCDG) is a commonly used granulation technique. Its low cost, fast production times and the ability to granulate hydrolysis-susceptible APIs have always been factors that favour RCDG for pharmaceutical manufacturing [1]. By nature, this process is an option for continuous manufacturing as feeding, processing and discharging of the product are done continuously. Previously, it was unsuccessful to measure the critical quality attribute granule size distribution (GSD) during a RCDG-process, as representative sampling of the product flow could not be linked with efficient GSD measurement while an in-line measurement reached capacity limits of the particle size analyser.

In this work, we joined representative sampling with a continuous GSD measurement by using dynamic-image analysis (Haver CPA 2-1, Haver&Böcker, Germany). To simulate the RCDG process, granules that were obtained using a roll compactor (BRC 25, L.B. Bohle, Germany) were conveyed using a vibrating funnel into an in-line rotary sample splitter (PT35-K, Vock Maschinen- und Stahlbau GmbH, Germany) at typical RCDG product mass flows. The sample obtained is directed into Haver CPA 2-1 and its particle size is estimated. Temporary measurement results are saved in regular intervals. Reference samples are split using a sample divider (Retsch, Germany) and measured using Haver CPA 2-1 in triplets. Our findings confirm the representative sample splitting using the PT35-K and a continuous measurement of GSD during the process (Figure 1a and Figure 1b).

To measure the particle size during RCDG the sample splitter and the particle size analyser will be assembled at the outlet of the roll compactor, allowing in-line sample splitting and subsequent particle size estimation. This method is a promising approach to continuous measurement of GSD during RCDG.

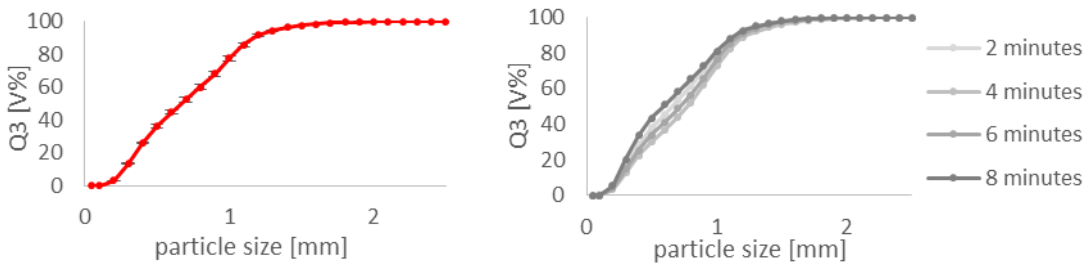

Figure 1. (a) Reference measurement (n = 3 mean ± sd), (b) In-line measurements (duration: 30 seconds each; n = 1)

[1] Swarbrick, James: Handbook of pharmaceutical granulation technology, Taylor & Francis Group, 2005

105. PHARMACEUTICAL EXCIPIENTS PROPERTIES AND THEIR IMPACT ON THE SCREW FEEDING PERFORMANCE OF CONTINUOUS PROCESSING LINES

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Screw feeder performance is a critical aspect in continuous manufacturing processes [1]. Pharmaceutical excipients, such as mannitol, microcrystalline cellulose, lactose monohydrate, and anhydrous dibasic calcium phosphate can present problems in ensuring a continuous stable feed rate due to their sub-optimal flow properties. The aim of this work was to identify and explain critical sources of variability of some powder excipients delivery by screw feeding, in particular to continuous processing lines. Pharmaceutical excipients with a wide range of material properties were selected, and they were evaluated by cylinder method, ring shear tester and powder rheometer (FT4) analysis. Screw feeder and hopper flow analysis were performed at different hopper fills and different screw speeds using a Brabender MiniTwin feeder (twin concave screw 12/12 mm, hopper volume 3.0 dm^3; speed max 140 rpm; Brabender Technologie, Germany). Several material properties were correlated to hopper flow and the capacity for screw conveying, as bulk density, compressibility index, flow function and parameters from FT4 dynamic downwards testing and dynamic upwards testing. Mannitol 200SD, Mannitol 100SD and Microcrystalline cellulose A200 showed the best screw feeder performance combining hopper flow and conveying by screw analysis. They have fair or passable flow character and bulk densities completely different, which influence on their feed rates. The lowest specific energy, effective angle of internal friction and cohesion values were observed for these powders. Mannitol 160C and calcium phosphate showed the highest feed rate values, due to their bulk densities, and highest values of stability index (SI). Mannitol 25C, Mannitol 50C and Microcrystalline cellulose C1000 showed the smallest feed rate values, the lowest SI values and poor screw feeder performance. Hopper flow is a bottleneck and needs to be overcome for the successful performance. The highest values of specific energy and effective angle of internal friction were observed for the samples with poor hopper flow. The study gathers valuable information about the screw feeder performance and input materials properties that can help process understanding and development of solid dosage forms in continuous process lines. [2]

[1] Stephen Byrn, Mauricio, Hayden Thomas, Eric Jaycock, Nicola Maron, Robert Mayer, Allan Myerson, Michael Thien, Bernhardt Trout. .Achieving continuous manufacturing for final dosage formation: challenges and how to meet them. May 20–21, 2014 continuous manufacturing symposium. Journal of Pharmaceutical Sciences, 104 (2015) 792–802.

[2] Bianca Aloise Maneira Corrêa Santos, Flavia Almada do Carmo, Walkiria Schlindwein, Carlos Rangel Rodrigues, Lucio Cabral, Gordon Muirhead, Julian Westrup, Kendal Pitt Pharmaceutical excipients properties and screw feeder performance in continuous processing lines: a Quality by Design (QbD) approach. Drug Dev & Industrial Pharmacy (2018).

106. MULTISCALE MODELLING OF TWIN SCREW GRANULATION USING A DEM–PBM COUPLING FRAMEWORK

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Twin screw granulation (TSG) is being widely adopted as a continuous pharmaceutical manufacturing process to reduce costs. In order to ensure the principle of Quality by Design within the TSG process, more scientific understanding of the particulate system behaviour is required in light of the overwhelming empiricism of TSG process design. In this study, a hybrid multi-scale modelling framework is developed to predict the granule attributes in the TSG, using the Discrete Element Method (DEM) to provide particle-scale physics and inform the process-scale Population Balance Model (PBM). Information is exchanged between the DEM and PBM models operating at different scales to extract the maximum benefits of the two different methods with complementary strengths. A coupling flowsheet between the hybrid DEM and PBM is proposed to demonstrate the coupling cycle in which the coupling mechanism, including building up the coupling interface and the multi-scale information passing, is described. The DEM–PBM coupling framework is built upon the commercial DEM code EDEM [1] and the commercial PBM code gPROMS [2]. The predictive capacity of the hybrid DEM–PBM coupling framework is examined with the experimental results from the twin screw granulator ConsiGma 25. This developed hybrid DEM–PBM coupling framework is applicable to a wide range of particulate processes, which provides a model-driven-design approach to the manufacturing of particulate products.

[1] DEM Solutions Ltd., EDEM 2017, (2017). https://www.edemsimulation.com/.

[2] gSOLIDS® 4.1 Release Notes, (2016). https://www.psenterprise.com/.

107. USING MIXER TORQUE REOMETRY FOR THE ASSESSMENT OF CHIA AS A BINDER FOR OBTAINING QUINOA GRANULES

Rosana Pereira da Silva, Jefferson Gaziro, Wily Edgardo Alayo Mendoza, Fanny Judhit Vereau Reyes, Alane Sousa Silva & Humberto Gomes Ferraz

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Quinoa (Chenopodium quinoa Willd.) and chia (Salvia hipanica) contain nutrients in abundance at balanced concentrations, providing fiber, protein, essential amino acids and vitamins. In the market, both cereals are available in capsule formulations, mix to dilute in juice or tablets. In the case of a fibrous material, and because of its high concentration in the formulations, for the production of tablets it is necessary to transform the material into granules. Thus, the objective of this work is to study the feasibility of using chia, in the form of powder, as a binder for the production of quinoa granules, in order to obtain a formulation from natural sources for consumption. In this sense, the mixer torque reometry (MTR) was used as a tool to study the concentrations of binder from chia and quinoa granulation, using a fractional experimental design to evaluate the influence of quinoa, diluent (microcrystalline cellulose) and the binder (chia) in obtaining the granules. The parameters selected were the ratio and maximum torque of the experiments and, an initial physical characterization of the chia and quinoa powders was performed by means of the particle size analysis, true density, apparent density and tapped density through the calculation of the compressibility index (CI) and Hausner Ratio (HR). Our results indicated that chia was important for obtaining the consistency of quinoa granules, presenting significant rheometric profiles in all experiments (Figure 1). With the aid of statistical analysis, it was possible to determine the granulation point of each test, selecting more suitable conditions for the production of homogeneous granules.

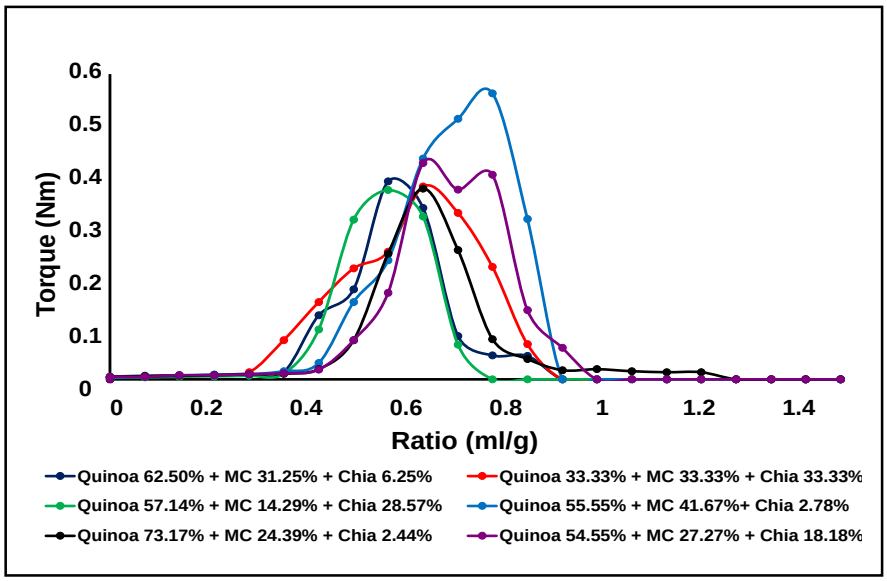

Figure 1. Multiple addition test in the MTR for different proportions of chia and quinoa

108. RHEOLOGICAL PROFILE IN MIXER TORQUE RHEOMETER OF SAMPLES CONTAINING FURAZOLIDONE AND DIFFERENT BINDERS

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Wet granulation is a process used in the pharmaceutical industry to improve raw materials flow and compressibility. The granules quality is related to the end point of granulation, being necessary to determine it with precision. Techniques based on the rheological profile of the samples were developed, directly relating the particles agglutination degree with the measured torque [1,2].

In this work, by means a statistical planning the influence of presence of microcrystalline celulose (MCC 101) and sodium lauryl sulfate (SLS) and the use of different binders on furazolidone process granulation, were evaluated by the rheological profile obtained in the Mixer Torque Rheometer MTR-3. The results indicated a significative influence of excipients MCC 101 and SLS on torque value, whereas the first increase, the second decrease it. The type of binder showed a slight significance, since sodium alginate led to higher torque values than polyvinylpyrrolidone K30. A formulation containing MCC 101 and alginate, without SLS was selected for further testing, to evaluate the binder concentration (1%, 2%, and 3%). As the level of alginate increase, higher torque values are obtained, indicating stronger particle agglutination. Granulates were produced following the liquid/solid ratio defined by MTR assays and then were characterized, demonstrating greater resistance and uniformity of the formulation with higher concentration of alginate. It is concluded that the MCC 101 and the higher concentration of alginate in formulation leads to granules with desirable characteristics, consistent with the results obtained in Mixer Torque Rheometer.

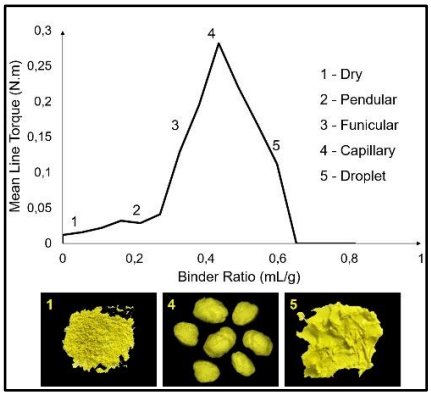

Figure 1. Rheological profile and steps of furazolidone granulation process

[1] B.C. Hancock; P. York; R.C. Rowe; M.D. Parker, Characterization of wet masses using a mixer torque rheometer, International Journal of Pharmaceutics, 102 (1994) 167-176.

[2] W.F. Sakr; M.A. Ibrahim; F.K. Alanazi; A.A. Sakr, Upgrading wet granulation monitoring from hand squeeze test to mixing torque rheometry, Saudi Pharmaceutical Journal, 20 (2011) 9-19.

109. MIXER TORQUE REOMETRY AS A TOOL TO OBTAIN THE IDEAL GRANULATION CONDITIONS OF CALCIUM CARBONATE

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Calcium is an important component for bone maintenance and, for the prevention of osteoporosis, is found in the form of food supplementation tablets containing calcium carbonate in the composition. However, since the formulation contains a high amount of elemental calcium (500 mg), the production of the tablets is quite dependent on the flow and compaction properties of the material, which results in uneven process performance. In this case, wet granulation is the most indicated process and the mixer torque reometry (MTR) can be employed as a tool to study the granulation characteristics of the different sources of calcium carbonate. Thus, the objective of the present work is to select the best conditions for wet granulation of different calcium carbonate samples, more specifically, calcium carbonate of mineral origin, oyster calcium carbonate and calcium carbonate from the algae Lithothamnium calcareum. For the design of the tests, a fractional experimental design was used, using microcrystalline cellulose as a diluent and gellan gum and pectin as binders. The parameters selected for evaluation were the ratio and maximum torque obtained in the experiments with the rheometer. The physical characterization of the calcium carbonate samples was performed through the tests of particle size, surface area, porosity and true density. Our results indicated that the samples are quite distinct as to their physical characteristics and, based on the statistical analysis, the best conditions for wet granulation of the different sources were selected (Figure 1), so that calcium carbonate is present in high quantity in the formulation, guaranteeing the production of tablets with lower weight. In conclusion, our results also indicate that calcium carbonate needs to be worked differently for each source, in order to ensure the obtaining of more adequate granules, thus facilitating the production of tablets.

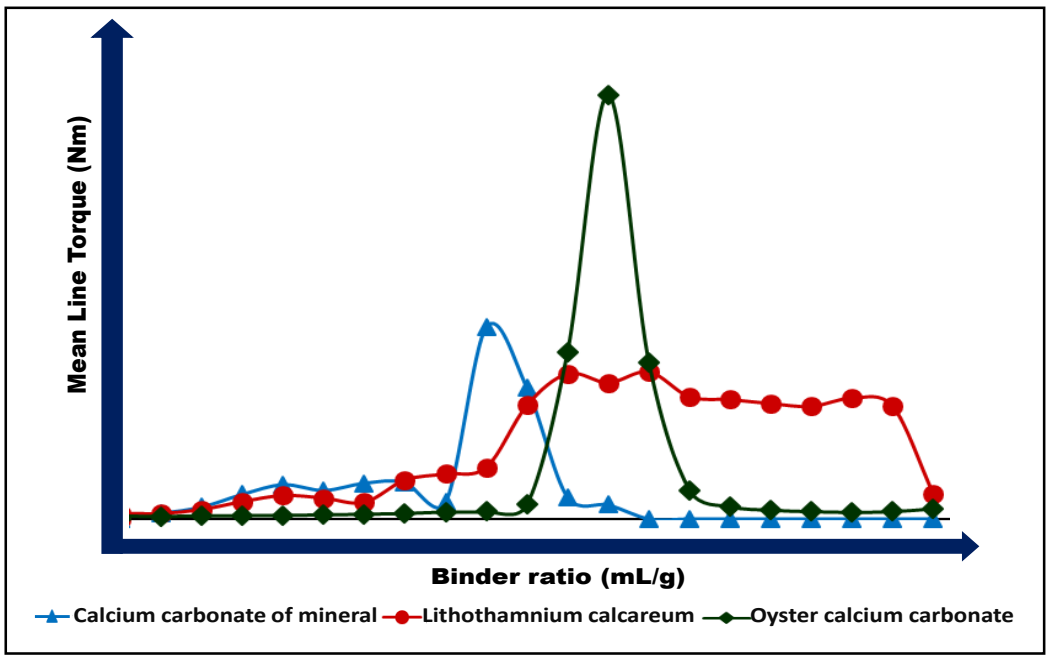

Figure 1. Multiple addition test in the MTR for different samples of calcium carbonate

110. RHEOLOGICAL EVALUATION OF MIXTURES CONTAINING PRAZIQUANTEL, MICROCRYSTALLINE CELLULOSE PH 101 AND DIFFERENT BINDERS

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The aim of this work is to evaluate, by Mixer Torque Rheometer (MTR), the rheology of mixtures of praziquantel with different amounts of microcrystalline cellulose PH 101 (Avicel® 101) and binders. Firstly, the method of water addition to a mixture containing praziquantel, Avicel® 101 and 5% of carrageen was developed through design of experiments. Since a slow addition of liquid gives stronger cohesion between particles [1], the chosen method consists in 30 additions of 0.5 mL of water to the mixture, which results in a torque value of 0.317 N.m. Then, another experimental design was evaluated, analyzing the effect of different proportions of Avicel® 101 (10, 20 and 30%) and binders (1% PVP, 1% alginate and 5% carrageen) in maximum torque and liquid-solid ratio when mixtures reach the capillary point of granulation. Surface-response graphs indicate that praziquantel has great limitations during granulation process and is strongly dependent of higher concentrations (30%) of Avicel® 101 to form appropriate granules. However, by using 5% of carrageen and reducing the concentration of diluent to 10%, it was possible to obtain rheological profiles with satisfactory values of L/S proportion and maximum torque.

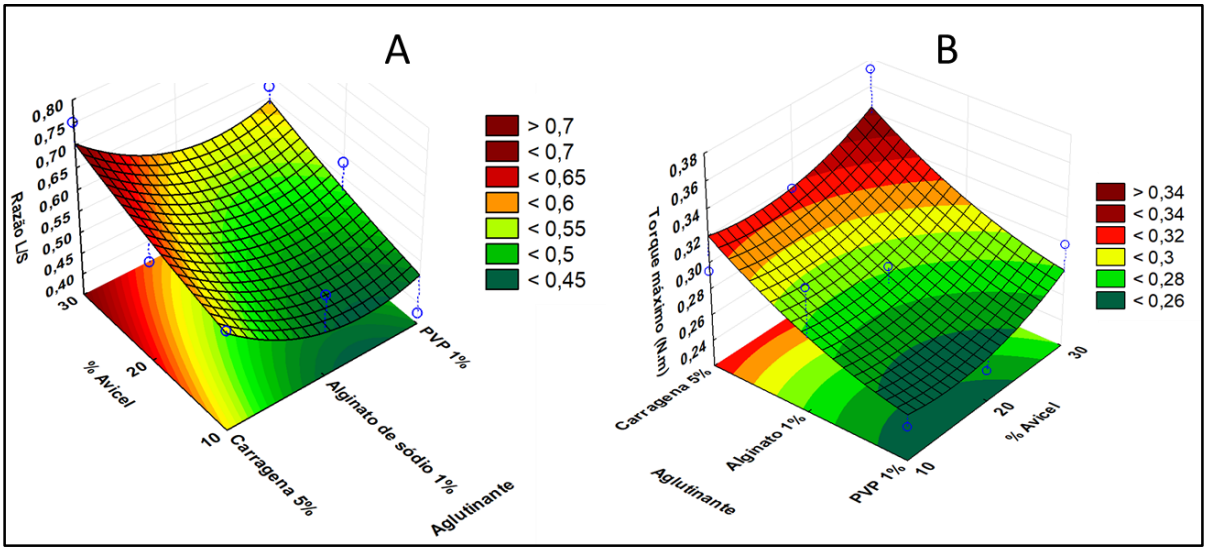

Figure 1. Three-dimensional response analysis showing the effect of amount of Avicel® 101 and type of binder over L/S proportion **(A)** and maximum torque **(B)** at capillary point in granulation process.

[1] M. Hariharan, M. Mehdizadeh. The use of mixer torque rheometry to study the effect of formulation variables on the properties of wet granulations. Drug development and industrial pharmacy, 28 (2002) 253–263.

111. MODELLING TWIN SCREW GRANULATION USING COMPARTMENTAL POPULATION BALANCE APPROACH

Hamza Y. Ismail[1,2], Mehakpreet Singh[2], Saeed Shirazian[2], Darren Whitaker[1], Ahmad B. Albadarin[1,2] & Gavin Walker[1,2]

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Wet granulation is one of the major steps in improving powder properties (flowability, friability, and size) in different industries including mining, fertilization, food production and pharmaceutical manufacturing [1,2]. Twin screw is continuous manufacturing operational unit used by pharma companies for granule production. Process parameters like liquid to solid ratio (L/S) and screw speed can influence the granule size produced from the twin screw granulator (TSG).

In this work, a compartmental population balance model (PBM) is developed as a predictive tool of particle size distribution (PSD) of granules produced from wet granulation in co-rotating twin screw where the PBM model is dependent on the L/S ratio and screw speed. This model accounts for aggregation and breakage of particles occurring in the five compartments (3 conveying zones and 2 kneading zones) of the TSG, and compartmental modelling is used to account for the inhomogeneity of the screw elements. Kapur kernel is incorporated in the aggregation rate and tested against sum kernel to check the kernel compatibility. Furthermore, the finite volume technique (FVT) is used for the first time to solve the numerical solution of the PBM, where the solution accuracy is dramatically improved as compared to the cell average technique (CAT). The empirical parameters in the aggregation and breakage kernels are estimated after performing optimizations to minimize the squared errors (SSE) between the model prediction and the experimental data collected. The experimental data are obtained for granulation of microcrystalline cellulose in 12 mm TSG by varying L/S ratios and screw speeds ranging from 0.9 to 1.3 and 50 to 200 rpm, respectively. The results show that aggregation is more dominant than breakage in all compartments, with aggregation rate being higher in conveying zones than kneading zones. It is also shown that the FVT predict the various results more accurately for Kapur's kernel than CAT.

[1] A. Chaudhury, H. Wu, M. Khan, and R. Ramachandran, "A mechanistic population balance model for granulation processes: Effect of process and formulation parameters," *Chem. Eng. Sci.*, 107 (2014) 76–92.

[2] A. Faure, P. York, and R. C. Rowe, "Process control and scale-up of pharmaceutical wet granulation processes: A review," *Eur. J. Pharm. Biopharm.*, 52, no. 3 (2001) 269–277.

112. AN INVESTIGATION INTO THE USE OF HOT MELT GRANULATION FOR THE MANUFACTURE OF FIXED DOSE COMBINATIONS.

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Granulation is considered as a main operation prior to the manufacture of pharmaceutical dosage forms such as tablets or capsules to ensure acceptable powder flow [1]. The recent emergence of twin screw extrusion (TSE) as a platform to manufacture pharmaceutical granules provides a non-ambient, solvent-free, continuous granulation method [2,3]. The aim of this study was to investigate the feasibility of using hot melt granulation (HMG) as a method to manufacture pharmaceutical granules containing a fixed dose combination of two antihypertensive drugs. Physical mixtures containing felodipine and losartan potassium as active pharmaceutical ingredients (APIs) at fixed ratio, Soluplus® and HPC as binders at different concentrations and microcrystalline cellulose (MCC) as a filler, were granulated using a 10mm twin screw extruder at different screw speeds and processing temperatures. It has been shown that the higher the concentration of the binding polymers, the greater the granule size (Figure 1). With respect to granulation processing parameters, the effect of screw speed was not pronounced at low processing temperature (110°C), nevertheless, when processed at high temperature, granule size was inversely affected by the screw speed with increased granule size being obtained at low screw speed. Optimized granules (by means of size and dissolution behaviour) were then tabletted and characterised for their dissolution behaviour which showed that drug release of both APIs was sustained over a period of 7 hours. Additionally, the formulation was able to improve the solubility of the poorly water soluble felodipine. This study clearly showed the feasibility of using hot melt granulation as a platform to manufacture fixed dose combinations.

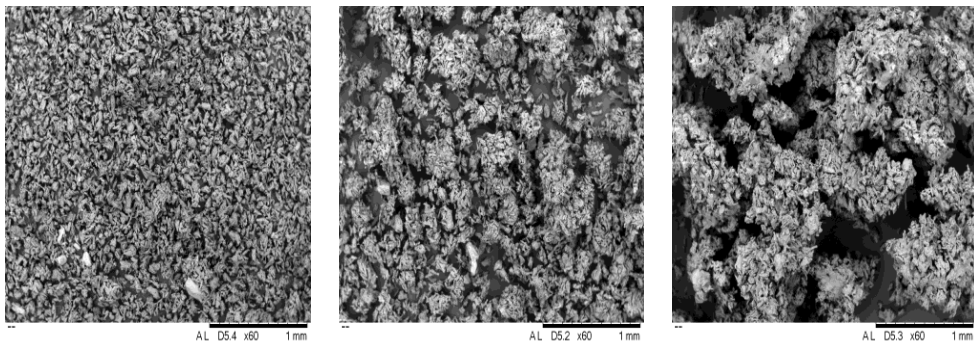

Figure 1. SEM micrographs illustrates the effect of polymer concentration on the granule size.

[1] S. Shanmugam, "Granulation techniques and technologies: recent progresses," vol. 5, no. 1, pp. 55–63, 2015.

[2] S. Weatherley, B. Mu, M. R. Thompson, P. J. Sheskey, and K. P. O 'donnell, "Hot-Melt Granulation in a Twin Screw Extruder: Effects of Processing on Formulations with Caffeine and Ibuprofen," *Assoc. J Pharm Sci*, 102 (2013) 4330–4336.

[3] A. Batra, D. Desai, and A. T. M. Serajuddin, "Investigating the Use of Polymeric Binders in Twin Screw Melt Granulation Process for Improving Compactibility of Drugs," *J. Pharm. Sci.*, 106 (2017) 140–150.

113. HOT MELT GRANULATION AS A PLATFORM TO MANUFACTURE AMORPHOUS SOLID DISPERSIONS WITH ENHANCED DISSOLUTION PROPERTIES

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The use of twin screw extrusion (TSE) as a platform to manufacture pharmaceutical granules is an emerging technique [1,2]. This concept takes advantage of the non-ambient nature of the melt extrusion, utilising meltable binders, which exhibit solid characteristic at ambient temperatures, but liquid properties during processing. The presence of these binders (at relatively low concentration) along with the solid components of the formulation will aid the formation of granules during hot melt granulation (HMG). This work aims to investigate, for the first time, the feasibility of continuous production of ASD using HMG.

Physical mixtures of the drug (Celecoxib (CX)), the polymer (HPMCAS) and the filler (microcrystalline cellulose (MCC)) was granulated using an open ended 10mm twin screw extruder operating at a screw speed of 10 rpm and a barrel temperature of 160°C. Interestingly, when using only drug and filler (MCC), granulation was not possible. Nevertheless, the presence of HPMCAS polymer in the formulation aided the formation of granules (Figure 1). It was also evident through particle size characterisation that the higher the concentration of the polymer (the binder), the larger the particle size. The results also showed, for the first time, that all obtained granules were amorphous (only drug amorphous) in nature suggesting the possibility of continuously manufacturing ASD using HMG despite the presence of low quantities of binding polymer. Dissolution testing of the obtained granules showed an improved dissolution behaviour when compared to the control formulation (Drug and MCC).
The study showed the feasibility of implementing twin screw melt granulation as a platform to continuously manufacture ASD.

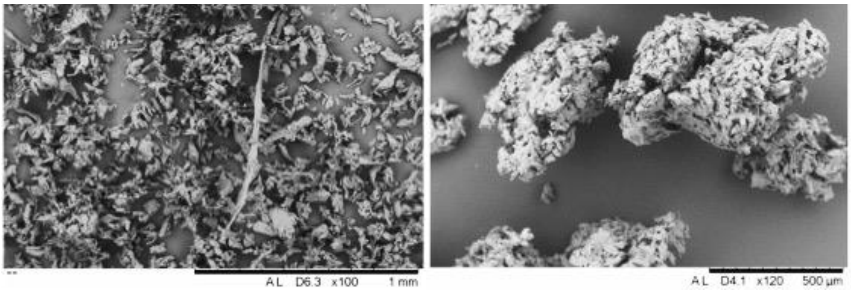

Figure 1. SEM micrographs illustrate the impact of the presence of the polymeric binder on the formation of the granules. Left: drug (CX) and filler (MCC), Right: drug, binder (HPMCAS) and filler.

[1] S. Weatherley, B. O. MU, M. R. Thompson, P. J. Sheskey, and K. P. O'Donnell, "Hot-Melt Granulation in a Twin Screw Extruder: Effects of Processing on Formulations with Caffeine and Ibuprofen," *J. Pharm. Sci.*, 102, no. 12 (2013) 4330–4336.

[2] D. C. T. Tan, W. W. L. Chin, E. H. Tan, S. Hong, W. Gu, and R. Gokhale, "Effect of binders on the release rates of direct molded verapamil tablets using twin-screw extruder in melt granulation," *Int. J. Pharm.*, 463, no. 1 (2014) 89–97.

114. NUMERICAL INVESTIGATION OF OPTIMUM HOPPER DESIGN FOR ROLLER COMPACTION PROCESS

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Dry granulation is a process where powder formulation is fed to counter-rotating rolls to form ribbons which are further milled to form granules. This process can be an easy alternative when wet granulation is not suitable for a given solid dosage formulation. The properties of ribbon not only depend on the formulation physical properties but also on the process conditions such as screw speed, roll speed, roll width, etc. Successful production of granules using dry granulation needs first and foremost uninterrupted powder supply from the hopper to the screw and then to the rolls. For this reason, hopper design plays a crucial role in this process. In this study, flow of powder from the hopper to the screw in a pharmaceutical roller compactor is investigated using numerical simulations. The objective of this study is to find the impact of hopper design on the powder flow to the screw. The hopper has a rectangular cross section, and consists of an impeller at the middle, whereas bottom of the hopper is connected to the horizontal screw which conveys powder to the rolls. The numerical simulations are performed using the discrete element method, which enables tracking of each and every particle trajectory through Newton's second law of motion.

Various simulation results were analysed and some of these include mass flow rate of powder, total force acting on the hopper walls vs mass holdup in the hopper, etc. These results are compared for two different hopper designs to evaluate the optimum hopper. In addition, the influence of impeller speed on the mass flow rate is studied. The total mass discharged over time for two different hopper designs is given in Figure 1, which indicates that design 2 yields better powder flow to the screw than design 1. It is also found that using the shortened impeller the powder flow rate to screw is improved (data not shown here). With this study, it is possible to select the optimum hopper design including the impeller for continuous flow of powder to the screw.

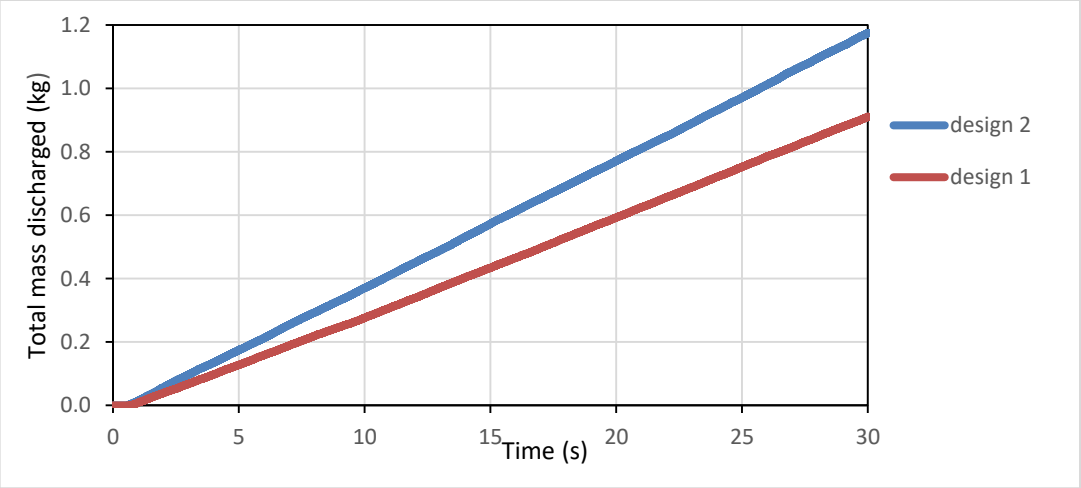

Figure 1. Total mass discharged from hopper to the screw over time.

115. COMPARISON BETWEEN TWIN-SCREW AND HIGH-SHEAR GRANULATION - THE EFFECT OF FILLER AND ACTIVE PHARMACEUTICAL INGREDIENT ON THE GRANULE AND TABLET PROPERTIES

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The aim of the study was to compare continuous twin screw granulation (TSG) with batch-wise high shear granulation (HSG). Two different formulations containing either microcrystalline cellulose and mannitol or microcrystalline cellulose and dicalcium phosphate as fillers were used. Three different active pharmaceutical ingredients (allopurinol, paracetamol and metformin HCl) were used as model substances. To find the suitable L/S ratio for the granulations, preliminary trials were carried out using a mixer torque rheometer. Both granule and tablet properties were characterised. Granules were characterized with respect to particle size distribution, flowability and morphology, while tablets were analysed for tensile strength and disintegration time. Both granulation techniques produced granules with unimodal particle size distribution after milling with the selected liquid to solid (L/S) ratios. Continuous twin-screw granulation was less sensitive for liquid amount than high shear granulation when comparing the granule size increase. Tablets made of TSG granules had a higher tensile strength than HSG tablets with all formulations (Figure 1). The findings confirmed that continuous twin-screw granulation is a good alternative to batch-wise high-shear granulation.

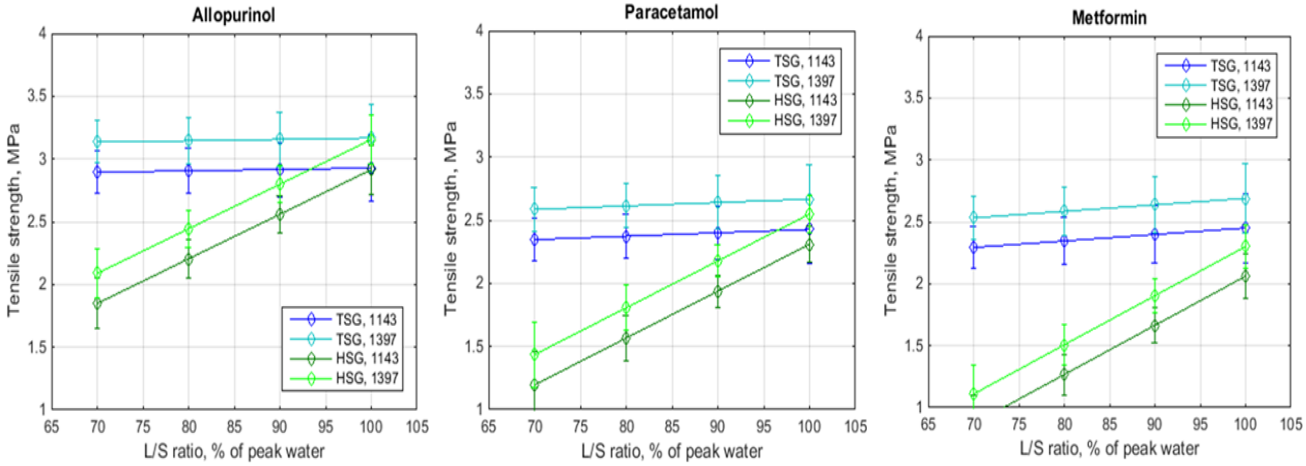

Figure 1. Tablet tensile strength as a function of liquid to solid ratio (L/S ratio) calculated from the highest torque in the mixer torque rheometer trials (% peak water).

116. OPTIMIZATION OF WURSTER FLUID BED COATING: MATHEMATICAL MODEL VALIDATED AGAINST PHARMACEUTICAL PRODUCTION DATA

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Wurster fluid bed coating is an effective way of manufacturing the layers used to create drug delivery systems, but it requires very precise control. On an industrial scale, the optimization of Wurster coating process parameters can be demanding because it necessitates many time-consuming pilot-scale experiments, the scope of which is limited by the cost of APIs (active pharmaceutical ingredients). To reduce the need for these experiments, we here develop a multi-scale mathematical model for faster and more reliable identification of the required coating process parameters.

We simulated the fluid bed coating of protective and active layers, using a Glatt GPCG 2 as a model fluidized bed system. Simple 'coating' experiments were performed with pure solvents (but without an API) to obtain the mass transfer coefficient of the solvent and heat transfer coefficients by fitting the outlet temperature. Resulting predicted outlet temperature and solvent content were evaluated with respect to sensitivity to input model parameters. We show that steady-state experiments are suitable for determination of heat transfer coefficients. However, mass transfer coefficient has to be evaluated from dynamic responses of the system to changes in inlet mass flow of coating medium and air flow temperature. Outlet air temperature was validated against existing production data involving the use of an API, and was found to be in good agreement.

117. UV IMAGING AS A TOOL FOR GRANULE DISSOLUTION MONITORING AND ITS COUPLING WITH STRUCTURE ANALYSIS VIA X-RAY MICRO TOMOGRAPHY

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The release rate of the active pharmaceutical ingredient (API) from granules during dissolution is one of the most important attributes of pharmaceutical granules [1]. The granule disintegration and dissolution behaviour depends not only on the granule composition and the intrinsic properties of the API and the excipients, but also on the granule particle size distribution and its internal structure, which is the result of the manufacturing process (roller compaction, fluid-bed granulation, high-shear granulation) and its parameters [2]. Since the granule inner structure also determines other granule properties such as mechanical strength, it is of interest to link the disintegration and dissolution behaviour with other measurable properties of granules [3].

This work deals with a model pharmaceutical formulation, consisting of ibuprofen as the API, lactose and microcrystalline cellulose as filler and pregelatinized starch as a binder, where water was added as liquid binder to the mixture during high-shear granulation. This formulation was subjected to a parametric study in a laboratory scale high-shear wet granulator. The structure of the produced granules (Fig. 1) was examined by x-ray micro computed tomography, while single granule dissolution experiments were conducted using the Sirius Surface Dissolution UV-Imager providing the real-time 2D UV maps of API concentration profiles in the vicinity of the granule. By coupling those two techniques, a toolbox for investigation of a granule structure-dissolution relationship was created and the granule properties were correlated with the granulation and formulation parameters.

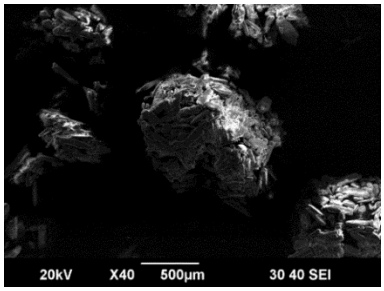

Figure 1. SEM micrograph of the granules.

[1] Kašpar O., Tokárová V., Oka S., Sowrirajan K., Ramachandran R., Štěpánek F., "Combined UV/Vis and micro-tomography investigation of acetaminophen dissolution from granules", Int. J. Pharm. 458 (2013) 272-281.

[2] Smrčka D., Dohnal J., Štěpánek F., "Dissolution and disintegration kinetics of high-active pharmaceutical granules produced at laboratory and manufacturing scale", Eur. J. Pharm. Biopharm. 106 (2016) 107-116.

[3] Smrčka D., Lesáková V., Dohnal J., Grof. Z., Štěpánek F., "Experimental analysis of inter- and intra-batch variation of granule porosity, stiffness and dissolution rate", Chem. Eng. Res. Des. 132 (2018) 1131-1142.

118. DEVELOPMENT OF AN ELECTROMAGNETICALLY ASSISTED SPRAY DRYING TECHNOLOGY

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Spray drying is the main process used for producing powders from a liquid feed. It has unique advantages, such as the ability to produce powders with a specific particle size and moisture content, handling heat sensitive products, and possibility of high volume application. In recent years, major focus has been given on understanding and modelling the spray drying process in order to facilitate the choice of operating conditions, which are product dependent, and to optimize energy usage. However, spray drying still remains a complex energy intensive process.

Spray drying is a convective drying method, which has low thermal efficiency. A liquid feed is atomized at the top of a drying chamber into a flow of hot air. For several products, this leads to a rapid reduction of surface moisture, which causes hindrance to moisture content transfer from the inner part of the particles. Consequently, a long drying time is required, which explain the generous height of industrial spray dryer chambers. Large volume of the chamber and long drying time make it difficult to control the morphology of the dry powder, and hence, reduce the quality of final product. Furthermore, a large volume of drying chamber leads to longer warm-up period, and makes the process complex, as a bigger hot air flow needs to be ensured.

Unlike the convective heating, electromagnetic drying is rapid and energy efficient, it promotes expulsion of inner water to the surface, and it allows selective heating of the materials depending on the local water content preventing damage to the surface and to the already dry area.

The goal of this work has been to improve thermal efficiency of the spray drying process by combining electromagnetic and convective heating. Such an improvement might aid development of a more flexible and sustainable process for the production of functionalized powders starting from a liquid feed. In this study, a new single-particle electromagnetically assisted drying-kinetics device is shown. It is based on a suspended drop method and it allows evaluation of the drying kinetics of a single-particle during combined convective drying and infrared (IR) energy. Effect of electromagnetic wave length and input power on drying kinetics of trial food feeds are presented. Potential of this novel methodology, such as focused and intermittent heating are also discussed.

Combination of electromagnetic energy and spray drying is a novel technology and it is expected to improve drying efficiency in food, pharmaceutical and chemical industries, and it could contribute to the development of innovative products in the powder form.

119. CHEMICAL OXYGEN DEMAND -- A KEY PARAMETER THAT SHAPES THE AEROBIC GRAULATION "LIFE CYCLE" AND GRANULE MICROBIOME

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As proposed by Trego *et al.* [1], there can be a predictable life cycle for anaerobic granules. A similar theory can potentially work for aerobic granulation as well and aerobic granules also go through a continuous process of core-formation, growth, maturing, breakage and re-formation. It has been found that influent chemical oxygen demand (COD) can be a key parameter that contributes the most to this life cycle and the microbiome structure in aerobic granules. Successful granulation can be achieved over a COD range from 500 mg/L to more than 5000 mg/L with satisfactory removal efficacy, although the granulation process varies. The life span of stable aerobic granules and the length of each life stage varies significantly with influent COD. With lower COD, it often takes longer time for the formation of mature aerobic granules, while the stable mature stage also lasts relatively longer. However, with high COD, a fast formation of aerobic granules could be achieved, but granules break down quickly when COD reached a certain limit. In addition, the microbiome population also varies significantly under different CODs, which may indicate that under different CODs, nitrogen and phosphorus removal can be done by different groups of microorganisms. To maintain an aerobic granular sludge system at the steady state, a diverse population of granules at various life stages will be ideal. To treat high strength wastewater with high COD, strategies such as alternate feeding with fluctuating COD can also increase the life span of stable granules.

[1] A. Trego, C. Morabito, S. Mills, S. Connelly, I. Bourven, G. Guibaud, C. Quince, Size matters for structure and function of anaerobic sludge granules, supporting a biofilm life-cycle model, 17th International Symposium on Microbial Ecology, Leipzig, Germany, August 12 - 17, 2018.

120. POWDER BED PACKING AND API CONTENT HOMOGENEITY OF GRANULES IN SINGLE DROP GRANULE FORMATION

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Single drop granule formation on a static powder bed of pharmaceutical mixtures was studied to investigate the effects of hydrophobicity and primary particle size distribution on the powder bed packing structure and the content homogeneity of active pharmaceutical ingredient (API) in granules formed. The granule formation mechanisms, drop penetration time, granule morphology and internal structure have been investigated previously in a mixture of microcrystalline cellulose (MCC) and acetaminophen (APAP), where with the increased APAP amount (decreasing particle size and increasing hydrophicity), drop penetration time increased, formation mechanisms transitioned from Spreading to Tunneling, the granules became smaller in size, and the internal porosity of the granules decreased [1]. In the current study, the powder bed packing structure was characterized by X-ray micro-CT and the API content uniformity was measured by UV-vis spectrometry. It was found that the internal structure became heterogeneous and there were dense aggregate regions in both the powder bed and granules from 25% APAP proportion, where the transition from Spreading to Tunneling occurs. With the increase of APAP proportion in the powder bed above 30%, the content uniformity of APAP (API ingredient) was compromised and the granules were starved of APAP. This was previously observed by other researchers [2] and was attributed to the preferential wetting of the ingredients. A regime map based on primary particle size and ingredient proportion was also attempted to predict the granule formation process. It is believed that the internal granule structure and API content homogeneity are influenced by both the primary particle size and wettability of the powder bed.

[1] T. Gao, A.S.S. Singaravelu, S. Oka, R. Ramachandran, F. Štepánek, N. Chawla, H.N. Emady, Granule formation and structure from single drop impact on heterogeneous powder beds, Int. J. Pharm. 552 (2018) 56–66.

[2] T.H. Nguyen, W. Shen, K. Hapgood, Effect of formulation hydrophobicity on drug distribution in wet granulation, Chem. Eng. J. 164 (2010) 330–339.

121. TWIN SCREW GRANULATION OF HORMONAL DRUG FORMULATION

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Granulation of hormonal drug formula was carried out in an automatic twin screw system (24mm diameter x 600mm length). The effects of twin screw configuration, geometrical parameters of individual components made of twin screws and operating conditions such as liquid to solid ratio and barrel fill on properties of granules were studied. It was found that the configuration of components in twin screws (disruptors, conveyors and kneading blocks) had a significant effect on properties of granules in terms of particle size, particle size distribution and density. A high number of kneading blocks in twin screws produced large granules (i.e. around 94% of granules >1mm in size) in "pasty" form. This is because high mechanical energy is imparted onto the wetted mass of powder, increasing high shear forces, compaction and distributive mixing. When only screw conveyors were used, the particle size distribution shifted to low sizes (i.e. only 34% of granules >1mm in size) however the particles were merely clumped together, without any sign of compaction. Granule porosity was also highly visible, which contributed to its low bulk density value in this case. It was also found that both liquid-to-solid ratio and barrel fill greatly affected the size and density of granules. High ratios of liquid to solid and degree of fill resulted in highly desirable bulk densities but produced coarse granules. It is clear that it is challenging to have relatively favourable granule densities, without compromising other essential properties, especially particle size distribution. Further studies should be done to strike a balance between granule properties, e.g. particle density vs. size distribution.

122. PARTICLE ATTRITION DURING PELLETING OF CORN STOVER: IMPACT OF MOISTURE CONTENT, RESIDENCE TIME AND PARTICLE SIZE

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The focus of the work is to understand how pelleting process variables impact particle attrition during pelleting of corn stover. In the present study, experiments were conducted by varying the initial particle size of the grind (6.35 mm and 11.11 mm grind) and moisture content (10, 15 and 20%, w.b.) and residence time (45, 90, 120 and 150 sec). The pellet properties measured include average mean particle size, d10, d50 and d90, % particle attrition (particles <425 microns in the pellets), pellet unit density and pellet durability. Models were developed for the process variable with respect to the pellet properties. Studies indicated that lower moisture content of 10% increases the particle attrition whereas increasing the moisture content to 15 and 20% (w.b.) decreased the fines in the pelleted material. Also, this study indicates that higher residence times of particles for 150 sec increased the particle attrition. At 10% (w.b.) moisture content and 150 sec residence time, the attrition values increased to about 26% for a 6.35 mm grind, whereas increasing the grind size to 11.11 mm decreased the attrition values to about 16-17 %. This study also indicates that the particle size distribution (geometric mean particle size, d10, d50, and d90) changes significantly with changes in the pelleting process variables. The unit density of the pellets decreased with increase in moisture content whereas the durability did not change significantly. The pellets are further analyzed using X-ray computed tomography (Fig. 1) combined with 3D image analysis to understand the effect of pelleting process variables on the total and connected crack volume, total dense features, and surface area to volume ratio to better understand particle attrition in pellets. These results indicate that medium to higher moisture (15 and 20%, w.b.) and lower to the medium residence time of 45 and 90 sec reduce total and connected crack volume and surface to volume ratio while increasing the total dense features in the pellets produced.

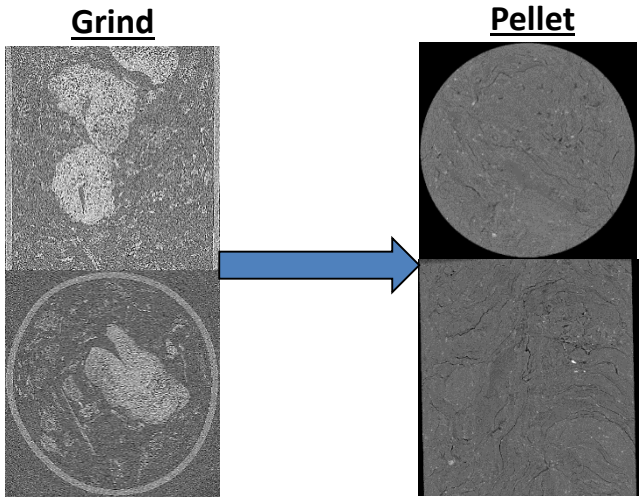

Figure 1. CT-scan image of raw and pelleted corn stover.

123. EFFECT OF FEED DRY MATTER CONTENT ON POWDER PROPERTIES OF MICELLAR CASEIN POWDER

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Micellar casein isolate (MCI) is a relatively new casein-based powder ingredient with a variety of functional properties, such as water holding capacity, gelling- and foaming ability. However, MCI powders have poor rehydration ability that impairs their application or functionality in the final product.

To better understand the rehydration behavior of this novel ingredient, in this work, the effect of feed dry matter content before freeze- and spray dried have been investigated. Increased feed dry matter from 12 to 18% influence pH, particle size distribution, and the rheological behaviour of the feed. The subsequent drying process, freeze- or spray drying, was found to be of great importance for the morphology and properties of the MCI powder, i.e. mean particle size diameter, morphology and microstructure evaluated by SEM (Scanning Electron Microscopy), colour and moisture content. Spray dried powders showed spherical particles while freeze-dried powders had a flaky shape. For the range of dry matter contents evaluated was observed that an increase of dry matter, increase feed viscosity resulting in powders with larger particles and darker colour after spray drying, but with significantly lower water contents.

The rehydration ability of MCI powders was evaluated in terms of wettability, dispersibility and final solubility. Wettability was higher for spray-dried powders compared with freeze-dried flaky powders. MCI powders produced from 12% DM feeds, both freeze- and spray dried powders, showed a significant improvement of dispersibility compared with the other DM contents. In general, the final solubility of spray-dried powders was better than freeze-dried powders. Spray dried powders were found largely solubilised (PSD < 5 μm) whereas freeze-dried powders contained particles in the size class area from 5 μm to 100 μm. This was possibly due to heat-induced changes in spray-dried powders and prolonged mineral re-equilibration for freeze-dried powders that exhibited lower pH than spray dried powders.

In conclusion, the results showed that it was possible to produce MCI powders with significant differences in powder properties and powder rehydration ability, by varying feed dry matter content and drying technique.

124. MICROSTRUCTURE BASED SIMULATION OF THE DISINTEGRATION AND DISSOLUTION OF PHARMACEUTICAL TABLETS

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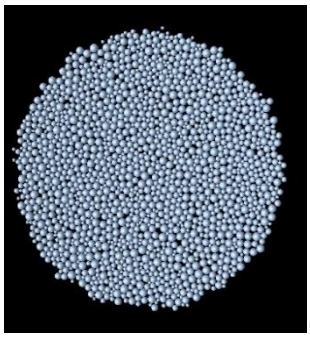
The development of pharmaceutical tablets or other dosage forms includes an interesting design problem: what values of formulation parameters that define the tablet shape, structure and composition should be used? The release of an active ingredient (API) from the tablet must follow a prescribed dissolution curve that relates the released amounts of API to particular times. The tablet characteristics determine the course of tablet disintegration and dissolution. Therefore it can be said that a particular dissolution curve is linked with particular formulation parameter values. However, in order to find the appropriate values of these parameters, numerous experiments are required.

In the present work, we study the disintegration and dissolution of a directly compressed tablet containing ibuprofen as an active ingredient, lactose as a filler and croscarmellose as a disintegrant. In the first part, the tablet is discretized into spherical elements and the discrete element method (DEM) is used to simulate tablet fragmentation triggered by the swelling of elements that represent the disintegrant component. The effect of disintegrant amount and disintegrant spatial distribution inside tablet on the resulting fragment size distribution is evaluated. The information about fragments obtained from the disintegration phase (e.g. fragment size and shape, the time when fragment was formed) is used as an input to the second part of the work, where the dissolution and the release of API to the surrounding solvent [1] is separately simulated for a statistically representative selection of fragments. These results are then superimposed and a complete dissolution curve is constructed. The computational simulation results are compared with experiments made in a dissolution cell including fragment size distribution evaluation by a dynamic light scattering apparatus.

Ultimately, a reliable methodology, able to simulate the process of tablet disintegration into fragments followed by individual fragments dissolution, can be used to predict the dissolution curve and therefore to reduce the number of experiments required during testing and development of new pharmaceutical products.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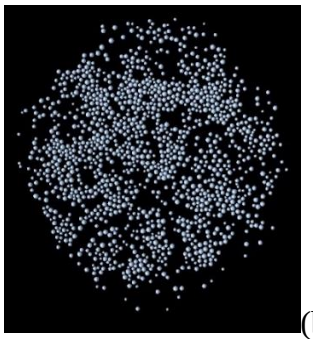
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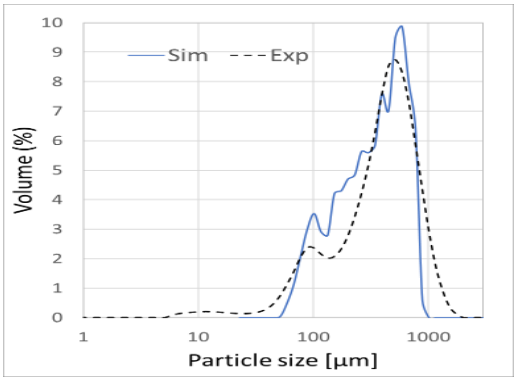

(c)

Figure 1. The tablet disintegration (a,b) and the example of resulting fragment size distribution (c).

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125. EXPERIMENTAL AND THEORETICAL STUDY OF SEMI-SOLID BINDER STICKINESS DURING A FLUID BED GRANULATION PROCESS

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Despite being a widely-used unit operation, the application of fluid bed granulation (FBG) is still to some extent guided by empirical methods rather than by scientifically-based strategies. The development of realistic mathematical models that are combined with suitable process measurements and evaluation can yield powerful tools for knowledge-based control of process and product quality. The complex interplay of various phenomena that govern the process dynamics of FBG at different scales poses a significant challenge in developing such models. Most importantly, a realistic FBG model has to incorporate phenomena associated with: (i) Hydrodynamic modeling of the multi-phase flow; (ii) Heat and mass balances: Impact of process conditions on the granule moisture and binder solidification; (iii) Modeling of contact mechanics and granule formation; (iv) Population balance (PB) modeling of agglomeration and breakage of multi-component granules.

It is well known that the moisture content (quantified as the Loss on Drying, LOD) has a strong impact on the granule growth rate during the FBG process. In our former studies [1,2] we have investigated the impact of the binder and solid properties on the growth rate. It has been also observed that the correlation between the LOD and the granule growth rate (or agglomeration rate constant) is not monotonous but typically goes through a maximum. This can be intuitively expected, because the main goal of the FBG process is to 'glue particles together'. From experience we know that every glue requires some acceptable range of its solvent content outside which it does not work properly – too dry or too diluted polymer solution does not adhere well. So, the 'stickiness' of the binder is a very important property to understand and to predict the effectiveness of a given binder in the FBG process.

This work is summarizing our recent effort in experimental and theoretical understanding of the binder stickiness. We will present the results of experimental measurement of the integral work of adhesion (W_{adh}) and the maximum adhesion force (F_{max}) for two polymeric binders – polyvinylpyrrolidon PVP and hydroxypropyl methyl cellulose HPMC – as function of moisture content in the range of 0 % - 50 % wt., using texture analysis (TA). We will show that a local maximum in both W_{adh} and F_{max} exists as function of moisture content, but its position depends on the polymer. Using the experimental data, we will explain FBG experiments showing that a maximum of granule growth rate exists for a particular LOD, which corresponds to the local maxima of the binder stickiness.

[1] Rajniak, P., Mancinelli, C., Chern, R., Štěpánek, F., Farber, L., Hill, B.: Experimental study of wet granulation in fluidized bed: Impact of the binder properties on the granule morphology, Intern. J. of Pharmaceutics, 334 (2007) 92-102

[2] Štěpánek, F., Rajniak, P., Chern, R., & Mancinelli, C.: Distribution and accessibility of binder in wet granules, Powder Technology, 189 (2009) 376-384.

126. EFFECT OF GRANULATION ROUTE ON TABLET DISINTEGRATION PATTERNS INVESTIGATED BY TEXTURE ANALYSIS

Jan Tomas[1,2], Jakub Dvořák[1,2], Ondřej Dammer[2], Marek Schöngut[2], David Smrčka[2], Josef Beránek[2] & František Štěpánek[1]

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The disintegration of a pharmaceutical tablet is a complex phenomenon that involves water penetration into the tablet structure, swelling of disintegrant particles, and loosening of inter-particle bonds. The disintegration rate depends not only on the tablet composition and the characteristics of primary particles (size distribution, surface wettability, solubility, compressibility) but also on the tablet manufacturing process (dry granulation, wet granulation, direct compression). Since efficient tablet disintegration is a prerequisite for the dissolution of active pharmaceutical ingredient (API) to the media, there is a need for proper characterisation of disintegration phenomena. At present, there are no predictive methods for tablet disintegration.

In the present work, we will demonstrate the usefulness of texture analysis [1] for the qualitative and quantitative characterisation of tablet disintegration processes. The disintegration cascade (Fig. 1) of a tablet recoded by texture analysis is very sensitive to the tablet composition and manufacturing route. In this work we will compare the disintegration patterns of tablets formed by direct compression with those produced by dry and wet granulation routes for an otherwise identical composition. We will explore the effect of intra- and extra-granularly added disintegrant, the ratio of the used disintegrants (croscarmellose or crospovidone) and the ratio of substances (API and excipient) in the tablet.

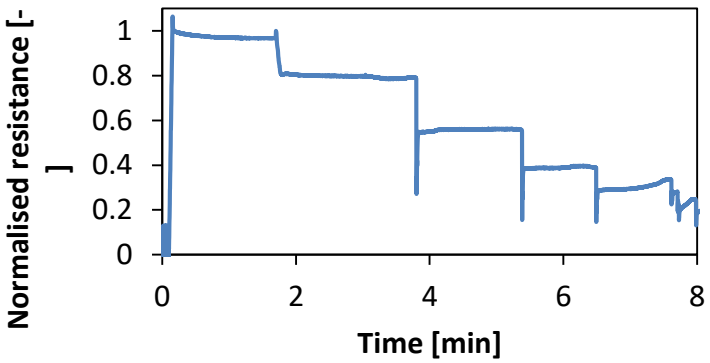

Figure 1. Typical sequence of disintegration steps recorded by texture analysis.

[1] J. Tomas, M. Schöngut, O. Dammer, J. Beránek, A. Zadražil, F. Štěpánek, Probing the early stages of tablet disintegration by stress relaxation measurement, European Journal of Pharmaceutical Sciences, 124 (2018) 145-152.

127. UNDOING GRANULATION: EFFECT OF FORMULATION PROCESS PARAMETERS ON THE SIZE DISTRIBUTION OF TABLET DISINTEGRATION FRAGMENTS

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The disintegration and dissolution of a pharmaceutical tablet can be thought of as reverse processes compared to granulation and compression. During granulation, primary particles of the active pharmaceutical ingredient (API) and excipients are put together by the application of a mechanical force (dry granulation) or a binder (wet granulation), and then compressed into tablets. During dissolution and disintegration, the tablet hierarchically breaks up into smaller fragments, which eventually dissolve. However, there is experimental evidence that the often-held assumption that tablets disintegrate into the granules they were compressed from, and these granules then disintegrate into the primary particles they were granulated from, is not always true. At present, there is no established theory that could relate the size distribution of tablet disintegration fragments to the tablet composition and its manufacturing process parameters.

The aim of this study is to systematically investigate the effect of the process route (dry/wet granulation or direct compression), disintegrant type and its placement in the tablet structure (intra- or extra-granularly) and the tablet composition (ibuprofen as API, lactose as excipient, and either croscarmellose or crospovidone as disintegrant) on the tablet disintegration process. The dynamic evolution of particle size distribution during tablet disintegration was investigated by dynamic light scattering, the evolution of internal tablet structure during disintegration was followed by magnetic resonance imaging (MRI) and the simultaneous release of the API (Fig 1). The relationship between the disintegration pattern and the tablet composition and manufacturing route is established experimentally and it is shown that the size distribution of the disintegration fragments does not necessarily replicate that of the underlying primary particles or granules.

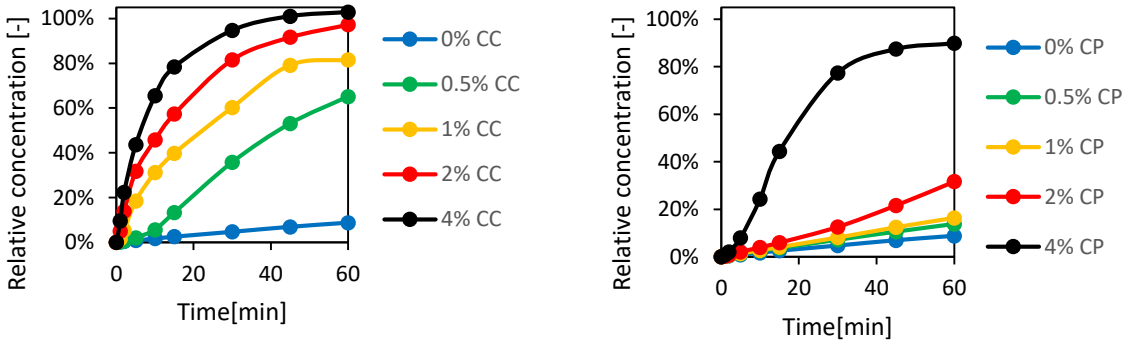

Figure 1. Comparison of disintegrant effect with 70% w/w of ibuprofen in a directly compressed tablet; A) croscarmellose; B) crospovidone.

128. REMOVAL OF PHARMACEUTICALS FROM WATER BY FILTRATOIN WITH ORGANOCLAY-BASED GRANULES

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The occurrence of organic micropollutants such as pharmaceuticals, personal care products, fluorinated surfactants, etc., in surface waters and drinking water supply systems has been detected in the last few decades. Quite a few micropollutans have a great potential risk for human health and environment, due to resistance to chemical, photolytic and biological degradation; high bioaccumulation and biomagnification potential in the food chain; great toxicity to wildlife; and long-range transport and distribution through the atmosphere and water bodies.

Sand filtration is included in the vast majority of Wastewater Treatment Plants as a system to reduce largely the amount of fine particles and the concentration of pathogens. The incorporation in such filters of a material with a great sorption capacity for organic micropollutants will permit their elimination or reduce considerably their concentration in the treated water. Modified clay-based composites may be a good alternative, but they should be incorporated in a 1-4% w:w ratio due to their low hydraulic conductivity. An alternative to increase the efficiency in the removal is the incorporation of this material as granules. In this work, the efficiency in the removal of several pharmaceuticals with different physico-chemical properties by filters made of sand/clay-based granules was examined.

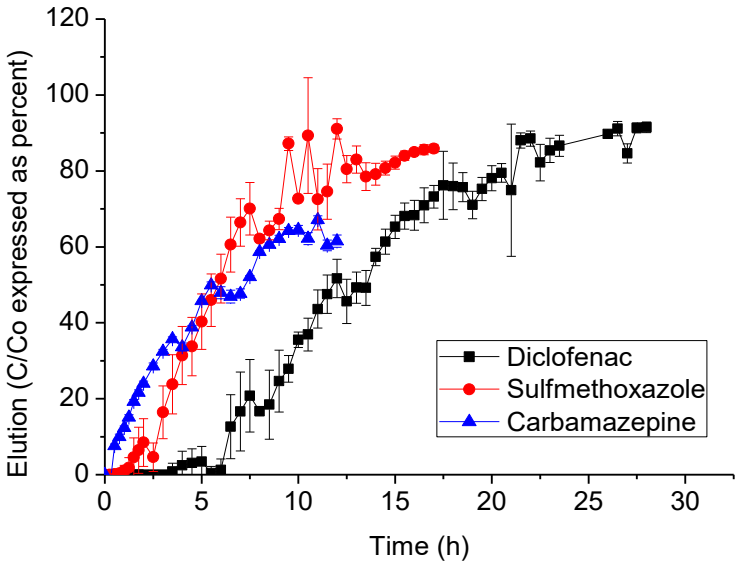

Figure 1. Removal of pharmaceuticals by filtration. The flow velocity was 1.19 m/h. Initial concentrations were 60 mg/L for diclofenac, 50 mg/L for sulfomethoxazole and 10 mg/L for carbamazepine. Clay-based granules/sand ratio 35% w:w.

129. METHOD DEVELOPMENT FOR REAL-TIME VISUALIZATION OF REHYDRATION OF CHEESE POWDER

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Cheese powder is utilized due to its flavour enhancement properties as a dairy ingredient in many food applications, such as snacks, soup, sauce and baked products. However, since it is made from one or more varieties of natural cheese, which contains 37-40% milk protein (intact proteins and peptides) and 40-47% milk fat, it is a multifunctional ingredient with e.g. water binding and emulsification properties. The differences in rehydration behaviour of different types of cheese powders is crucial for understanding the water binding and emulsification mechanism for application in real food systems.

The common microscopy techniques for visualization of rehydration of dairy powders are light microscopy [1] and scanning electron microscopy [2]. However, the previously studied dairy powders are milk protein concentrated powders. For a powder with high content of fat, such as cheese powders, these microscopy techniques are not capable of providing information of the change of fat fractions during rehydration. Therefore, in this study, we aim to develop a real-time confocal laser scanning microscopy (CLSM) method for following the rehydration of twelve types of cheese powders, where the fluorescent dyes Fast Green FCF and Nile Red are used to label the protein and fat fractions respectively. In this way, the details of how protein and fat interact with water or oil can be elucidated. The results from a pre-trial has showed different behaviour (i.e. article swelling or dispersion/disintegration) of cheese powder particles depending on whether emulsifying salt was added during production or not. It was also seen that much fat was rapidly dispersed into the water phase as fat droplets, with the remaining fat fraction being entrapped in powder particles or closely associated to aggregated particles. Image analysis will be applied to quantify the difference among the twelve types of cheese powders during the rehydration process. Moreover, methods for characterisation of powder properties, such as solubility, wettability, and particle size will also be carried out to supplement the results from the microscopy method.

[1] A. Mimouni, H.C. Deeth, A.K. Whittaker, M.J. Gidley , and B.R. Bhandari, Investigation of the microstructure of milk protein concentrate powders during rehydration: Alterations during storage, Journal of Dairy Science, 93 (2010) 463–472

[2] S.V. Crowley, B. Desautel, I. Gazi, A. L. Kelly, T. Huppertz, J. A. O'Mahony, Rehydration characteristics of milk protein concentrate powders, Journal of Food Engineering, 149 (2015) 105-113

130. TWIN SCREW GRANULATION: HOW DO PRIMARY POWDER CHOICE AND STORAGE CONDITIONS EFFECT GRANULE AND TABLET CHARACTERISTICS?

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Within the pharmaceutical industry, a shift towards continuous processing of granules via wet granulation, away from traditional batch-wise techniques is underway. Twin Screw Granulation (TSG) is a continuous process which, in recent years, has been the subject of much research to increase knowledge in its role within solid oral dosage form manufacturing.

The aim of this work was to investigate primary powder choice and storage conditions in order to maximise granule compressibility and tablet strength. Six powders of varying solubility, particle size and hygroscopicity were chosen for testing purposes. Granules were produced and stored at constant temperature and a range of relative humidity before producing tablets under increasing compressive forces at 2, 14 and 28 days.

Tablets were also produced immediately after the TSG process and before drying. Tablets were stored under the same conditions and tensile strength tested at the same time intervals as the granule batches. The tablets produced immediately after granulation showed an increase in strength over those produced from stored granules for some materials, an example is shown in Fig 1 for lactose (Pharmatose 200M®). It is hypothesised that rather than Van der Waals forces and interlocking that occurs during dry tabletting, contacts between wet particles become solid bonds as the bridges dry and the dissolved content crystallises producing a stronger compact when produced with wet granules.

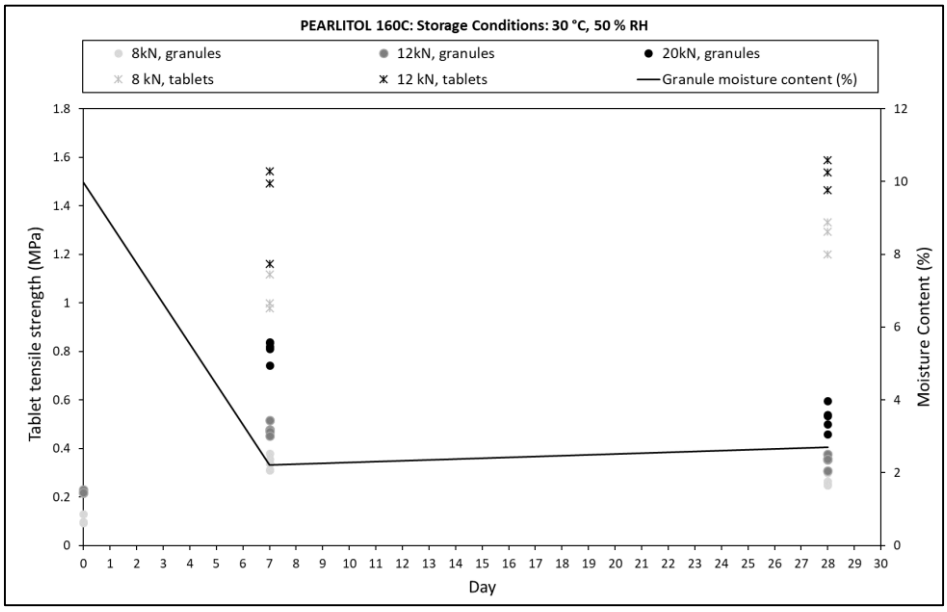

Figure 1. Showing tensile strength of stored Pharmatose 200M® granules and tablets that have been produced at 8, 12 or 20 kN.

131. PREPARATION OF SOLID DISPERSIONS WITH RESPECT TO THE DISSOLUTION RATE OF ACTIVE SUBSTANCE

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One of the current problems in pharmaceutical industry is a poor water-solubility of the active pharmaceutical ingredients (APIs). A large number of used APIs has very low solubility in aqueous media. Hence, improving the solubility of APIs is often a key point of the formulation strategy. The preparation of solid dispersions (SDs) is one of well-established methods to improve the solubility of APIs, but it may present additional challenges in terms of their preparation and stability. SDs can be used as any advance substitution of granules with a uniform internal structure. SDs are commonly a binary API-polymer system, where API is molecularly dispersed in a polymeric matrix.[1]

The aim of this work was to prepare SDs by solvent evaporation and spray drying method. The prepared SDs were compared with the physical mixtures (PMs) in terms of their dissolution properties. Tadalafil was used as a model poorly water-soluble drug, which was mixed with three different hydrophilic polymer matrices, Kollidon® VA 64, Kollidon® 12 PF and Soluplus®. First, amorphous SDs were studied using different dissolution techniques, at Wood´s apparatus and open loop flow-through cell apparatus (USP 4). Collected samples were analyzed using HPLC after the dissolution. Furthermore, the SDs were characterized by X-ray power diffraction (for determination amorphous sample) or Fourier-transformed infrared spectroscopy (to determine interaction between tadalafil and polymers) and their stability was also assessed.

It was confirmed that hydrophilic polymers have significant influence on the drug release from binary mixtures (SDs or PMs). The type of hydrophilic polymer can control if the drug release is either immediate or prolonged. Our results show that as the molecular weight of polymer increased, hydrophilic polymer more swollen and on the contrary the drug release decreased. In this case of SDs it means, that the presence of both Kollidons has a positive effect on the acceleration of tadalafil release, on the other hand, the presence of Soluplus® retarded its release. This results lead to different use in pharmaceutical industry.

[1] Huang, Y.; Dai, W. Fundamental aspects of solid dispersion technology for poorly soluble drugs. Acta Pharm. Sin. B, 4 (2014) 18–25

132. DEVELOPMENT OF FINITE ELEMENT MODEL TO PREDICT THE BEHAVOUR OF BILAYER TABLETS DURING UNIAXIAL TENSILE TEST

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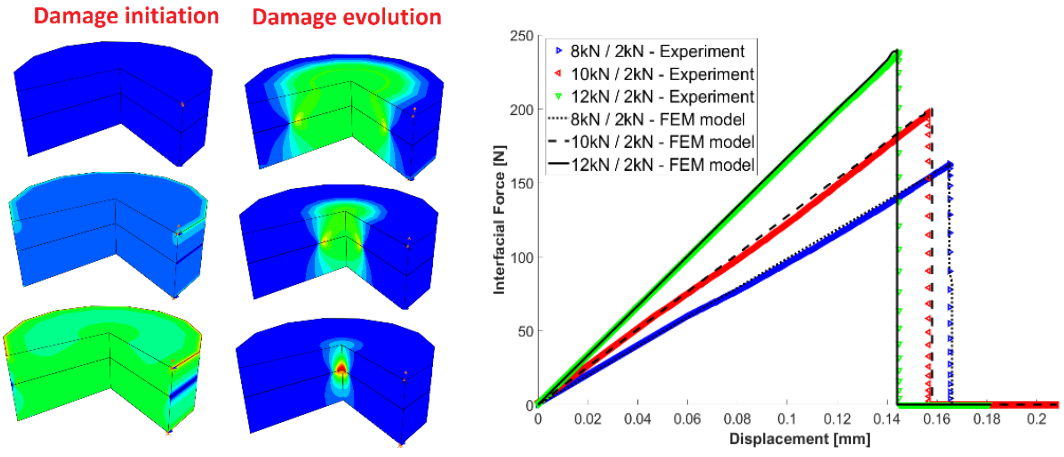
The manufacture of bilayer tablets although successful for several years, still needs improvement to ensure that the manufacturing process satisfies therapeutic specifications and regulatory requirements. The main challenge is to ensure that bilayer tablets possess both a specific mechanical strength and a low packing density, to ensure that it is sufficiently strong to maintain its integrity during handling and transport while simultaneously weak enough to satisfy the dispersion and dissolution requirements for pharmacological administration. Bilayer tablets are prone to fracture by delamination along the interfaces between the layers, because of their associated inherent binding weakness. The adhesion-cohesion interaction as subsequent of binding weakness on the interface of bilayer tablets has not been intensively investigated to date. In this work, such fundamental mechanisms underlying crack propagation on the interface of bilayer tablets during a uniaxial tensile test were investigated. A strategy using a computational platform by hybridizing Finite Element Method (FEM) and Cohesion Zone Model (CZM) to predict whole interfacial force-displacement relationship, as well as fracture energy of bilayer tablets during the uniaxial tensile test was developed. The strategy was validated against experimental force-displacement data by means of uniaxial tensile tests of bilayer tablets using various separation speeds. After the linear elastic extension of the two layers, the interface separation was found to be dependent on the separation speed of the tensile test.



a) b)

Figure 1. a) Prediction of normal pressure in bilayer tablets using FEM; b) Verification of FEM by experimental data

133. USING GRAPHENE OR GRAPHENE OXIDE TO IMPROVE THE PHYSICAL QUALITY OF GRANULATED FERTILIZERS

Shervin. Kabiri[1], Roslyn J. Baird[1], Ivan.Andelkovic[1], Rodrigo C. da Silva[1], Fien Degryse[1], Dusan Losic[2] & Michael J. McLaughlin[1]

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2 School of Chemical Engineering, Engineering North Building, The University of Adelaide, Adelaide, SA 5005, Australia
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Fertiliser granules need to have sufficient mechanical strength to resist fracturing and creation of dust during handling, storage and spreading. Graphene (GN) and its oxidized form graphene oxide (GO) are new materials with distinctive properties such as unique 2D structures, high surface area and exceptional mechanical properties.[1] Graphene is the toughest material ever measured and it has the capability to enhance the mechanical properties of many composites materials.

Cogranulation of low doses (0.05 to 0.5% w/w) of GN or GO sheets significantly enhanced the mechanical properties of monoammonium phosphate (MAP) granules. Inclusion of 0.5% GN and GO enhanced the crushing strength of amended granules 18 and 8 times, respectively. Cogranulation of GN also improved the resistance of MAP granules to abrasion and enhanced impact resistance. The advantages of GN and GO sheets in enhancing the mechanical properties of MAP granules were related their high specific area, superior filler-matrix and interlocking ability arising from their 2D geometry. These results highlight the potential for GN/GO additives to enhance the physical properties of granulated fertilizers.

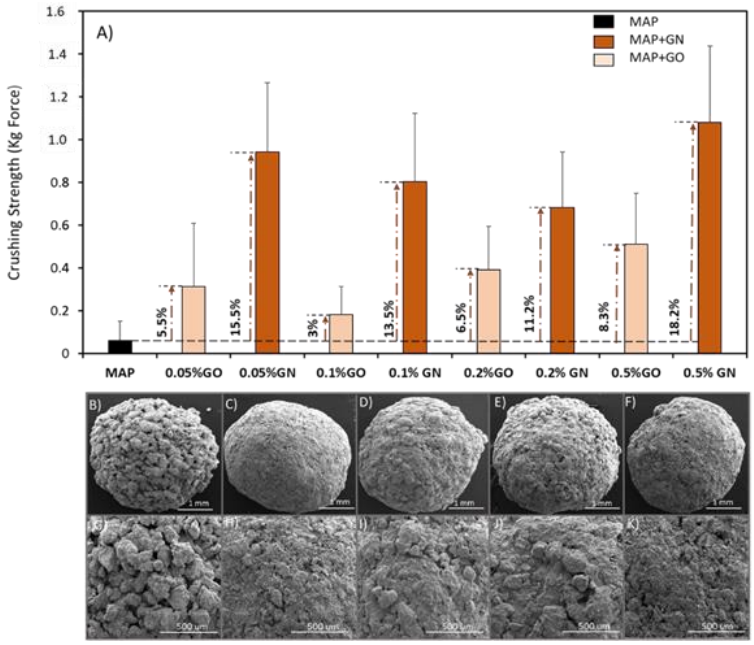

Figure 1. Force required to crush a granule of mono ammonium phosphate (MAP) with different concentrations (0 to 0.5%) of graphene (GN) or graphene oxide (GO) and high and low resolution SEM images of the granules.

[1] Zhu, Y.; Murali, S.; Cai, W.; Li, X.; Suk, J. W.; Potts, J. R.; Ruoff, R. S. Graphene and graphene oxide: Synthesis, properties, and applications. Advanced Materials, 22 (2010) 3906-3924.

134. THE ROLE OF MOLECULAR WEIGHT OF AMORPHOUS FRACTION IN AMORPHOUS/CRYSTALLINE MIX REHYDRATION

Chiamaka C. Nnaedozie[1], Constantijn F.W. Sanders[2], Edgar Chavez Montes[3], Laurent Forny[4], Gerhard Niederreiter[4] & Agba D. Salman[1]

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Powder rehydration is influenced by a number of factors particularly powder properties like molecular weight of amorphous powders. The powder properties influence powder wetting and overall rehydration. This study assesses the effect of molecular weight on the rehydration of an amorphous and crystalline powder mixture. Three grades of maltodextrin of different molecular weight: Maltodextrin DE39, Maltodextrin DE19 & Maltodextrin DE6 and Lactose 100M were used. Each grade of maltodextrin powder was mixed with lactose and rehydrated in a mixing vessel at a water temperature of 20°C.

For each rehydration experiment, changes in particle counts was tracked using an FBRM probe. Overall rehydration time was determined as the time it took to reach 10% of maximum particle counts. Powder sinking was monitored using video recordings. Additionally, the recordings were used to obtain qualitative information about the process, particularly, rehydration issues like lumping and sedimentation. The powder/liquid interaction was summarized in regime maps. Floating limited rehydration is more predominant with mixtures with maltodextrin with higher molecular weight. Molecular weight of maltodextrin plays an important role in the sinking and overall rehydration of the lactose/maltodextrin mixtures.

135. EFFECTS OF STORAGE CONDITIONS ON PHYSICOCHEMICAL PROPERTIES OF SPRAY-DRIED CAMEL MILK POWDER

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2 Faculty of Food Science & Technology, Nong Lam University, Vietnam
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Due to high content of bioactive compounds in camel milk and limited geographical distribution of camels, it is necessary to produce camel milk powder so that it can be made available all over the world. In this study, changes in physiochemical properties of camel milk powder produced by spray drying as they were stored at 11.15, 22.26 and 32.27% relative humidity (37^{o}C) over 18 weeks were investigated. At predetermined time intervals (0, 3, 6, 9, 12, 15 and 18 week), the powder samples were withdrawn and analysed in terms of colour, true density, rehydration properties (wettability, dispensability and solubility), particle size, structural transformation (X-ray), morphology (SEM), glass transition temperature, T_g (DSC), and fat oxidation (GC-MS). The X-ray results showed that the fresh spray-dried camel milk powders were amorphous and that there was almost no structural transformation during storage. It was impossible to detect T_g under DSC scan of the fresh samples. However, after 3 weeks of storage, due to reduction in moisture content and a_w, and structural relaxation, T_g of powder could be determined. During storage, true density, colour in terms of L*, a*, whiteness were almost unchanged while the browning (b* value), fat oxidation and particle size (D[3,2]) of powders increased, and rehydration ability slightly decreased. For these criteria, except for fat oxidation, the samples kept at 33.27% RH were affected to a greater extent than those stored at 11.15 and 22.26% RH. Overall, spray-dried camel milk powder still retained its properties at 11.15% RH up to 18 weeks.

136. DEFORMATION AND STRENGTH OF COMPRESSIBLE GRANULES

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Accurate descriptions of the mechanical interactions between compressible particles are required to assist in the production of granules with desirable properties and the design of associated granulation and handling processes. However, contact laws and granule strength models relating particle properties to underlying material properties remain underdeveloped for such particles. In this work, finite element simulations are used to investigate the influence of particle material characteristics on the strength and load-displacement response of compressible granules. A fully-customisable elastoplastic constitutive model is utilised to describe granule macroscopic behaviour, allowing compressive, shearing and dilatory plastic flow; increase of elastic stiffness with density; and nonlinear hardening. Parametric studies are carried out exploring an envelope of material properties obtained from instrumented die compaction testing for a range of pharmaceutical powders and granules [1]. A hybrid linear-exponential contact law is established, while a quadratic model is proposed to relate material characteristics to contact law parameters. Applications of this work to granule design to predict macroscopic properties of granules are presented.

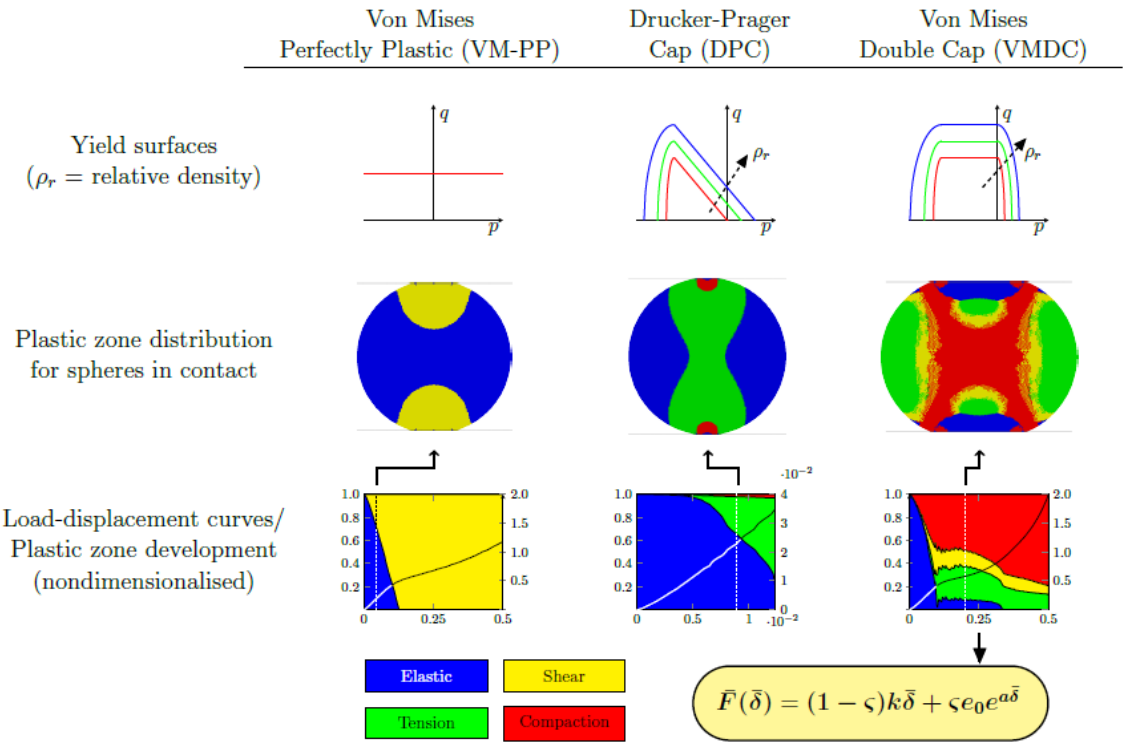

Figure 1. Relationship between compressible plasticity model (top), plastic zone development (centre) and particle load-displacement response (bottom) for three compressible plasticity models

[1] J. Cunningham, K. LaMarche, A. Zavaliangos. Modeling of powder compaction with the Drucker-Prager cap model, in Predictive Modeling of Pharamaceutical Unit Operations (2017) 205-217.

137. MECHANICAL PROPERTIES OF CEREAL BARS EXPLAINED BY PARTICLE MOVEMENT ANALYSIS

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2 Nestlé Research Centre, P.O. Box 44, 1000 Lausanne 26, Switzerland
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Cereal bars are common breakfast snacks for a broad range of the population. They are characterised by their specific dual texture, both chewy and crunchy. The texture is correlated to the mechanical properties of the product. This paper presents a new way of assessing and explaining the mechanical properties of a cereal bar focusing on the movement of the particles occurring during compression and cutting tests at different loading rates. The product studied is a Nesquik® cereal bar, a rectangular compacted material composed of large spherical particles of low density in the millimetre range, linked by a highly viscous organic binder. The sugar binder is the main element contributing to the chewy texture, while the crunchiness is the result of the brittle cereal particles. Another aspect studied in this paper is the movement of the particles during consumption playing a role in the mechanical properties and thus in the texture of the product. The mechanical tests are performed using geometries and speeds which are close to the actual consumption process. Three loading rates are used in order to observe the effect on the mechanical response. The motion of the particles is analysed by particle image velocimetry (PIV). It has been found in this study that PIV is a relevant tool to explain the mechanical behaviour of a cereal bar. The bars tested under different loading rates exhibit different load-displacement curves, and this difference can be visualised with the PIV. Moreover, the significant influence of the loading rate on the mechanical properties of such a product leads to a conclusion that instrumental testing for prediction of textural properties needs to be done in consideration of the test speed.

138. EFFICIENT POWDER DISPERSION AT A STATIC AIR-LIQUID INTERFACE

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The dispersion of dehydrated powders in water is a key step in many process industries. During the dispersion process, the powder grains often form heterogeneous lumps that are wet outside and dry inside, the presence of which reduces the efficiency of the overall dispersion process. Often it is difficult to predict and control the conditions under which lump formation occurs, relative to the efficient dispersion of individual powder grains. To address this, the balance of forces and the motion of the grains after contacting the liquid surface have been the studied [1–2].

The present contribution is an experimental study of the continuous addition of grains to an air-liquid interface. Depending on factors such as grain size, density and wettability (governed by its contact angle as well as the liquid surface tension), the surface is found to support a single or several layers of grains, forming a stack. The floating of stacks is governed by the grain contact angle, ratio of bulk and liquid density and Bond number. Stack detachment and lump creation is shown experimentally to be favoured by grains with high contact angle and smaller particle size and this can be explained by the different effect of the Bond number on the dispersion of individual grains and the collapse of a granular island into a dry lump.

These findings can help promoting dispersion of powders into liquid and avoiding lump formation during the reconstitution of dehydrated food, pharmaceutical and detergents.

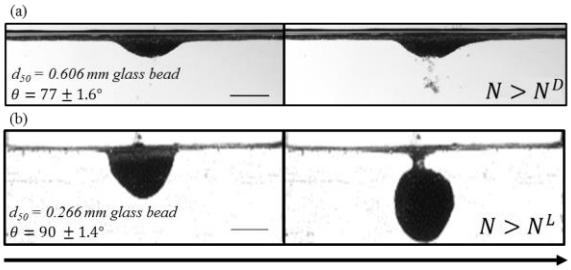

Figure 1. Different mechanisms limit the size of the granular islands obtained by pouring grains continuously onto an air-liquid interface. The top images show the sedimentation of grains occurring when the liquid is able to impregnate into the pores within the grains. The bottom images shows the detachment of a stack from the interface, leading to lump formation.

[1] P. S. Raux, H. Cockenpot, M. Ramaioli, D. Quéré and C. Clanet, Wicking in a Powder, Langmuir, 29, 11, (2013) 3636–3644.

[2] D. Vella, P.D. Metcalfe, R.J. Whittaker, Equilibrium conditions for the floating of multiple interfacial objects, Journal of Fluid Mechanics, 549 (2006) 215–224.

139. RECONSTITUTION OF MALTODEXTRINS: INTERPLAY OF MOLECULAR WEIGHT AND POWDER ADDITION RATE

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Dehydrated food powders with poor dissolution can dramatically compromise food processing, with consequences for the final product quality and the consumer experience [1-2]. In this study, the reconstitution performance of amorphous food powders is characterised with and without water agitation, using three analytical techniques (optical, conductimetry and refractive index probe). Carbohydrates and milk powders were used as model systems. The effects of moisture content, molecular weight, particle size, agitation speed, mass flow rate and liquid temperature on the dissolution process were considered.

The limitations and capabilities of the optical characterisation are discussed and confronted with conductivity and refractive index probes. Conditions under which water can impregnate into powder pores without forming strong films at powder-liquid interfaces were identified. Whereas higher liquid temperature improved the dissolution of low-molecular weight carbohydrates, it worsened the wettability of food powder with high-molecular weight. Whenever powder wetting was the rate determining step, the dissolution performance is found to improve with a slower flow rate.

The understanding provided by this work can be used during product reformulation, to avoid a deterioration of dissolution performance.

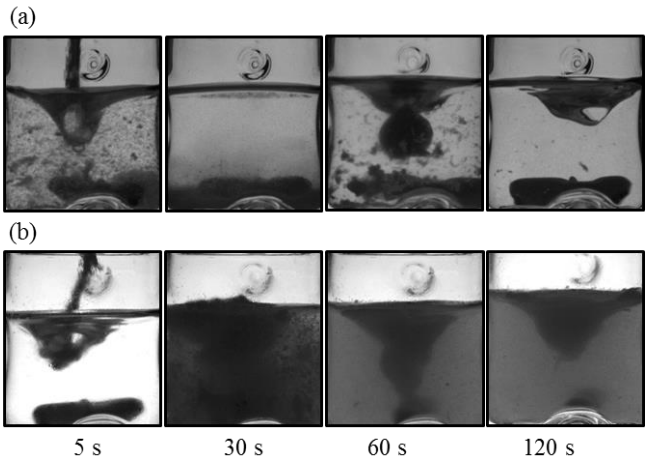

Figure 1. Air entrainment and lump formation of maltodextrin DE21 from the sediment layer (top images) and lump formation of maltodextrin DE2 float on the interface (bottom images) at (500 rpm, 22℃) agitation.

[1] J. Dupas, L. Forny, M. Ramaioli, Powder wettability at a static air-water interface, Journal of Colloid and Interface Science, 448 (2015) 51-56.

[2] J. Dupas, V. Girard, L. Forny, Reconstitution properties of sucrose and maltodextrins, Langmuir, 33 (2017) 988–995.

140. ONLINE MONITORING OF POWDER MIXING USING AN OPTICAL CAMERA

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Dry powder mixing is a crucial step widely used in food, pharmaceutical and chemical industries. In order to monitor the mixing process online, many devices were used, such as near-infrared (NIR) probes, chemical imaging cameras and optical cameras. Among them, NIR probes output one signal at a time to indicate the mixture composition within the monitored area, chemical imaging cameras requires long time to acquire an image of the mixture within the monitored area, while optical cameras are outstanding because of its high resolution, short image acquisition time and convenience.

When using an optical camera to online monitor the dry powder mixing, image processing techniques are required to extract information about the mixing process [1–3]. In this paper, two indications (A and B) were used. Indication A was used to represent the mixture composition at time by using a value extracted per image. Indication B was used to represent the mixing efficiency during a time length by using the average of values extracted per pixel.

Experimentally, a high-speed optical camera was used to online monitor the mixing process of coffee and creamer in an Eirich Intensive Mixer. By using indications A and B, the end points of mixing with different coffee ratios (1%, 3%, 5% and 10%) were determined.

[1] G. Grasa, J.C. Abanades, A calibration procedure to obtain solid concentrations from digital images of bulk powders, Powder Technol. 114 (2001) 125–128.

[2] J.G. Rosas, M. Blanco, A criterion for assessing homogeneity distribution in hyperspectral images. Part 1: Homogeneity index bases and blending processes, J. Pharm. Biomed. Anal. 70 (2012) 680–690.

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141. INVESTIGATING THE FLOATING BEHAVIOUR OF FOOD PARTICLES

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Powdered food products, such as coffee, milk powders, infant formula and malt beverages are of tremendous importance for the food industry. A central quality attribute of these products is a fast and complete reconstitution [1]. However, unsatisfactory reconstitution performance is frequently observed. Floating of powder on the air-liquid interface plays an essential role in this context. Particle floating is determined by the force balance of gravity, buoyance and capillary force. Especially for small particles, floating behaviour is increasingly influenced by the wettability of the solid [2,3].

In this work, floating behaviour of food particles of varying wettability was studied. Floatation experiments with single particles were performed to directly measure particle immersion depth. The use of spherical particles (rotationally axisymmetric) allowed a comparison of experimental results with an established theoretical model of a floating sphere. Discrepancies between experimentally determined and predicted immersion depth were observed. The obtained results form a basis for the implementation of an advanced model which takes properties of real food materials into account. This will ultimately enable the prediction of floating behaviour of materials with direct relevance to the food sector. The importance of wettability on floating behaviour was also demonstrated in this study.

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[2] J. Dupas, L. Forny, M. Ramaioli, Powder wettability at a static air-water interface, Journal of Colloid and Interface Science, 448 (2015) 51‑56.

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142. EFFECT OF PARTICLE COATING ON THE PERFORMANCE OF FOOD POWDERS

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The surface of food powders is one of the most important factors driving powder functionalities such as flowability, hygroscopicity and reconstitution. Particle coating has been applied in the food industry as way of engineering particles and modifying the powder physical and physicochemical properties.

In this study, coating of food particles was performed and its effect on different powder properties was examined. The process parameters were optimized to minimize particle sticking and agglomeration and enhance the coating. All samples were conditioned prior to characterisation and their water activity was determined using thermal treatment to accelerate equilibration [1]. Scanning electron micrographs allowed the particle visualisation before and after the coating treatment. Quantification of the coating was performed by measuring the electrical conductivity of reconstituted samples and comparing it with the reference material. Characterization of the powder functional properties showed improved material performance depending on the process parameters applied.

[1] M. Dupas-Langlet, J. Dupas, S. Samain, M.-I. Giardiello, V. Meunier, L. Forny, A new method to determine “equilibrated” water activity and establish sorption isotherm by erasing surface history of the samples, Journal of Food Engineering. 184 (2016) 53–62.

143. PROCESS → STRUCTURE-PROPERTY RELATIONSHIPS ON POWDER AGGLOMERATION AND PERFORMANCE

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In the processing and handling powders, particle interactions inevitably occur, often leading to cohesiveness and undesirable agglomeration, with consequences on performance such as powder flow, dispersability, dissolution, stability and overall quality of the final product. In this study, the use of physicochemical and surface analytical characterization techniques provided information on particle-property modification resulting from processing. These particle-property attributes resulting from different unit operation conditions were examined in relation to their effect on performance features associated with changes taking place at the surface. Interfaces and surfaces provide the primary framework for particle cohesion-adhesion interactions, including the dependence of such interactions on surface roughness, solid-state properties and humidity conditions. Collective input from the physicochemical, thermodynamic, visual and rheological methods provide information on the nature and impact of agglomeration at different length scales. Processed materials such as the pharmaceutical excipients commonly used in industry, starch and lactose, and beverage products such as coffee and chocolate, were used for this study. This presentation discusses the use of multi-parametric information, derived from various experimental analytical tools, to obtain information on the structural diversity and evolution associated with the processing of powders. The study covers pharmaceutical and food relevant materials, including the impact of processing on overall powder performance.

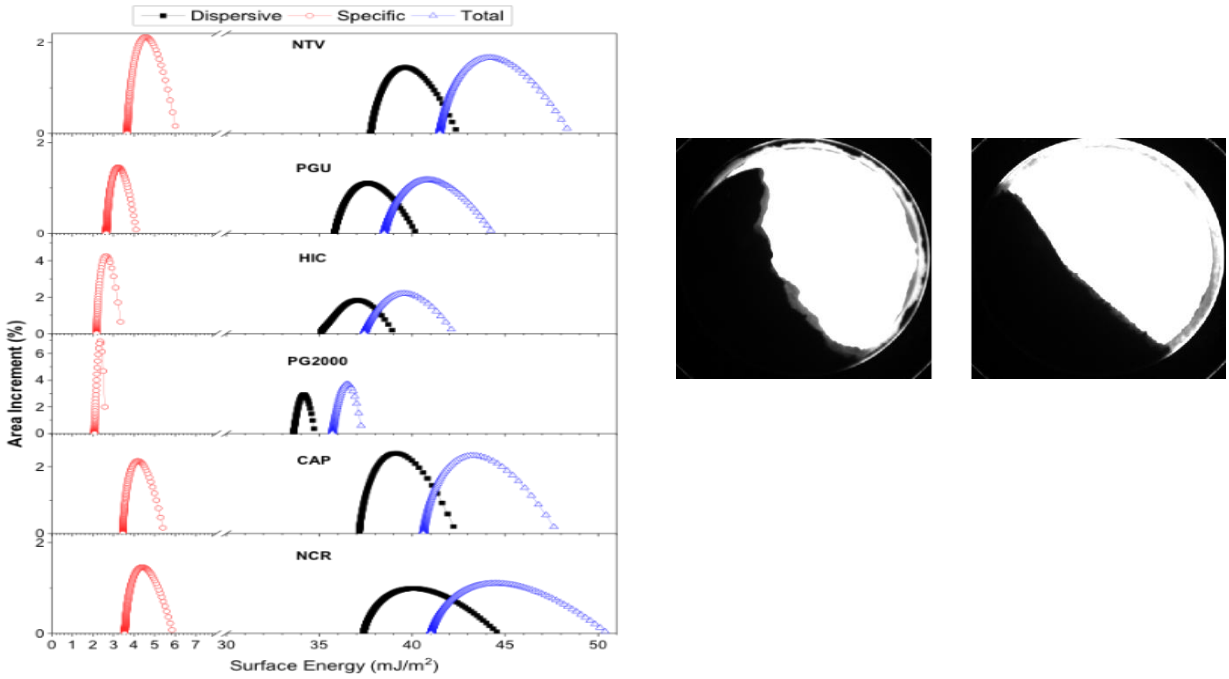

Figure 1. Surface energetics, roughness and powder flow

144. EXPERIMENTAL VALIDATION OF A DEM-SIMULATION ON THE MIXING BEHAVIOUR IN A SPHERONIZER

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Extrusion-spheronization is a common process to produce spherical pellets of uniform size and shape for pharmaceutical purposes. The size and shape distribution of a batch is influenced by how particles move inside the spheronizer. These movements can be determined by DEM simulations. However, experimental data is necessary to validate these findings.

In this work, experiments concerning the mixing behaviour in a spheronizer were conducted and the results were compared to DEM simulations [1]. In both cases, binary mixtures of coloured particles were used. The concentration of the coloured particles at the outer spheronizer wall and its change over time is shown in for the experiments and the simulation.

At the beginning of the experiment, blue particles remain on the bottom and red particles on top. The rotation of the friction plate induces a twisted-rope-like motion of the pellet bed [2], transporting red pellets from the top to the bottom, as can be seen in , part (1) to (3). The simulated data matches the experimental data for the progression of mixing quality. However, experimental results show a delayed change in concentration, indicated by the different time scales in . This can be explained by the slow acceleration of the friction plate in the experiment, where the set speed was reached only after completed mixing. The simulation however started with a constant plate speed, and particle motion was already in a steady state.

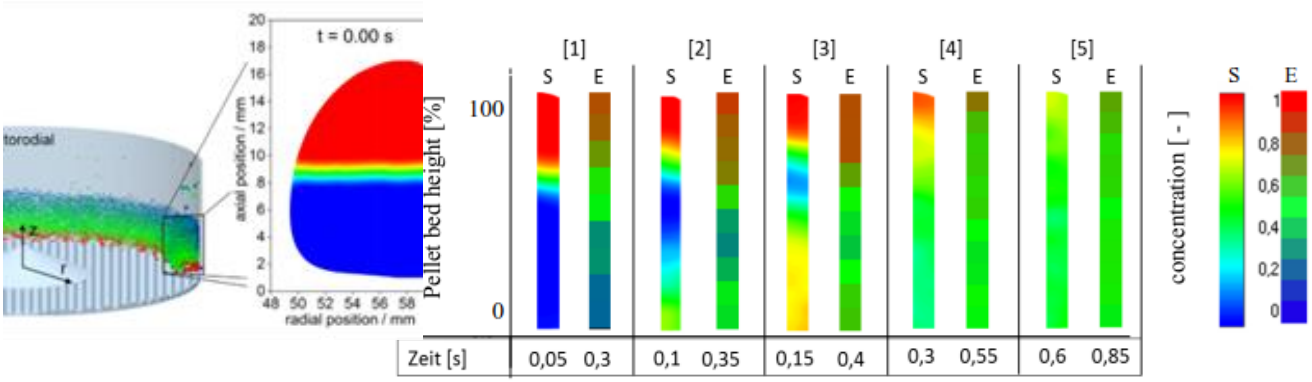

Figure 1. comparison of concentration of coloured particles at to the outer wall of the spheronizer for different time. "S simulation; "E" experimental results.

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[2] M. Köster, M. Thommes, Analysis of particle kinematics in spheronization via particle image velocimetry, European Journal of Pharmaceutics and Biopharmaceutics, 83 (2013) 307-314

145. CONTROLLING OF THE MIXING BEHAVIOUR OF DRY COHESIVE PARTICLES

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Mixing of granular material is important in several multicomponent particulate processes such as concrete preparation, chemical formulation, nuclear and pharmaceutical engineering. However, under the presence of shear, granular materials in these processes often have a tendency to segregate owing to differences in particle properties such as the size and density. In this work, we investigate the effect of tunable cohesive strength on the mixing of dry granular systems.

First, particles are made cohesive via extensive chemical silanization. The cohesive strength of the particles depends on the reaction duration of the silanization process. Particle-particle cohesion force is measured using an in-house micro-positioner device and particles surface is characterized using AFM. Then, rotating drum experiments are performed and cohesive particles are mixed with non-cohesive particles. Finally, we investigate the mixing of non-cohesive particles mixed with cohesive particles under different cohesion strengths and particle sizes.

This work demonstrates the ability of cohesion to improve particulate mixing in dry systems. We found that high cohesive force clumps the small particles together and hence weakens the percolation segregation.

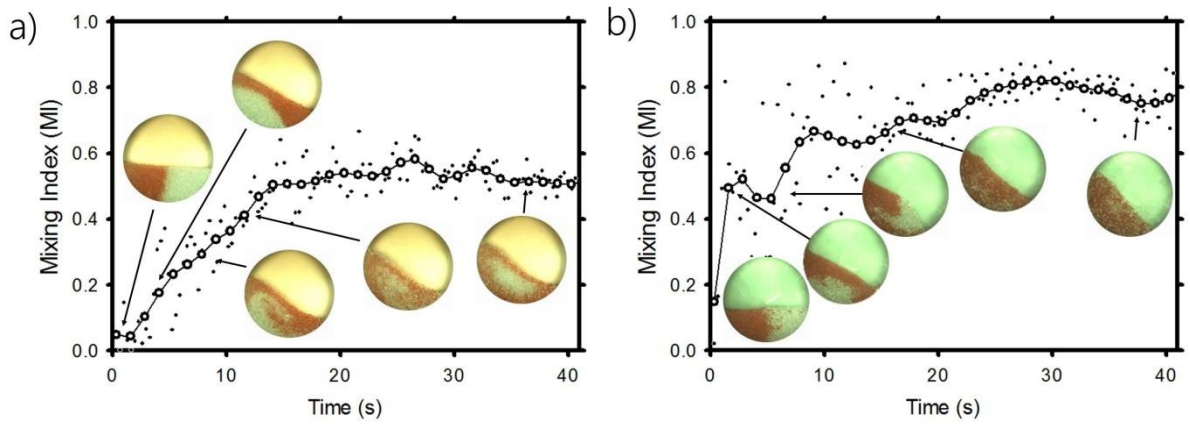

Figure 1. Mixing index as a function of time for (a) non-cohesive system and (b) cohesive systems.

146. THE INVESTIGATION OF HYDRATE-ANHYDRATE TRANSFORMATIONS USING RAMAN LINE-FOCUS MICROSCOPY

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Compounds of pharmaceutical interest have often the ability to form different solid forms that can influence the physical, chemical and mechanical properties of a drug. It is vital that there is sufficient knowledge regarding the thermodynamic landscape of these forms and their transformation mechanisms in different conditions because uncontrolled solid form transformations have been shown to be a root cause of many product withdrawals. [1] Consequently, these transformations can have an uncontrollable in vivo impact. Therefore, the aim of this study was to obtain particle level understanding of the nature of hydrate-anhydrate transformations using an imaging method based on Raman line-focus microscopy.

In this work, an individual particle of carbamazepine dihydrate (CBZD) was used as a model system. The dihydrate form (orthorhombic) of CBZ was identified using differential scanning calorimetry (DSC), thermal gravimetric analysis (TGA), x-ray powder diffraction (XRPD), and compared to the Cambridge Structural Database (CSD). Single crystal dehydration of CBZ dihydrate was monitored using a Linkam hot stage (heating rate of 5 K/minute) and an in-house built Raman microscope based on a line-focus method (785 nm, 256 pixels, 2 cm-1 resolution). Multivariate curve resolution (MCR) was applied to the data. The combination of the solid-state analytical methods used confirmed the solid form of CBZ to be CBZD (CSD ref code: FEFNOT01). Using MCR, four different forms of CBZ were identified using a single particle of CBZD, between 35-90 °C. The Raman spectra showed well-defined features of CBZ and the anhydrate phase, as well as the indication of two less stable intermediate anhydrate form I of CBZ (Figure 1). In conclusion, the Raman line-focus method showed the potential of explaining the dehydration of solvated species using only a single particle.

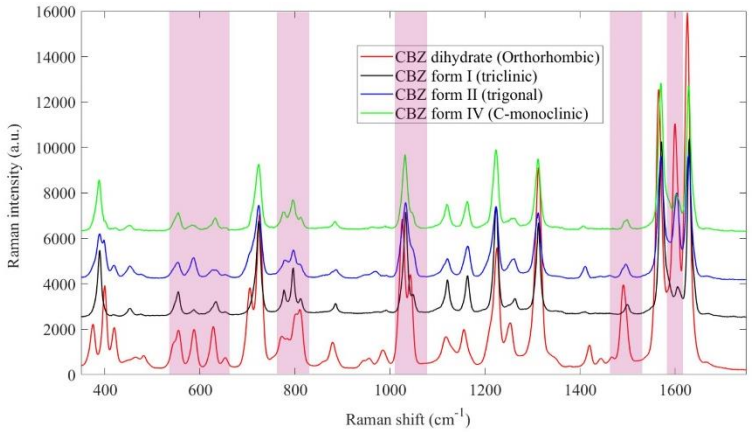

Figure 1: Raman spectra of CBZ solid-state forms obtained from

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147. AN INVESTIGATION INTO DISTRIBUTION NUCLEATION IN FLUIDISED BED GRANULATION USING THE PARTICLE COATING NUMBER IN A SMALL SCALE FLUIDISED BED SYSTEM

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Nucleation is an important rate process in wet granulation, which occurs when a powder first comes into contact with a liquid binder, and primary nuclei are formed. Research has shown that nucleation in wet granulation often plays a significant role in determining the size and structure of the final granules. Nucleation can take place via two mechanisms, according to the binder droplet/particle size ratio: immersion nucleation and distribution nucleation. A regime map has been developed by Hapgood in 2003 [1] for immersion nucleation, however relatively little is known about distribution nucleation. To quantify distribution nucleation, the particle coating number (Φp) was derived by Kariuki et al in 2013 [2] (Eqn 1). This parameter predicts the fractional coverage of binder over a particle surface.

$$\varphi_p = \frac{6\, X_{LS}\, a_d}{\pi\, d_d^3\, \rho_d\, A_{SA}} \qquad \text{Eqn 1}$$

Where XLS is the liquid–solid mass fraction, ad is the droplet foot print , ASA is a specific surface area of the particulate material , dd droplet diameter and ρd is the liquid density.

The ultimate aim of this work is to develop a new conceptual theory to describe and predict the the distribution nucleation mechanism in fluidised bed granulation. In this study, fluidised bed granulation experiments were conducted in two lab scale fluidised beds with cylindrical and conical columns, to gain better understanding of the effects of varying process parameters and material properties. Glass beads of different sizes were used as model powder materials, and these were granulated with aqueous solutions of Hydroxypropyl methylcellulose (HPMC) with assorted molecular weights, to vary viscosity without significant changes to contact angel and surface tension.

The results show that increasing the atomising pressure has a clear effect on nuclei formation, due to the reduction in droplet size. Increasing the liquid flow rate resulted in an increase to both granulated fraction, and the size distribution of granules. Post-spray mixing time had a strong effect on the granule size distribution, with granule size increasing for times up to 2 min. Additionally, binder viscosity and fluidising gas velocity had strong effects on granule size, while increasing the mean size of the starting material resulted in reduced nuclei formation.

[1] Hapgood, K. P., Litster, J. D., & Smith, R. Nucleation regime map for liquid bound granules. AIChE Journal, 49(2) (2003) 350–361.

[2] Kariuki, W. I. J., Freireich, B., Smith, R. M., Rhodes, M., & Hapgood, K. P. Distribution nucleation: Quantifying liquid distribution on the particle surface using the dimensionless particle coating number. Chemical Engineering Science, 92 (2013) 134–145.

148. OPTIMISATION OF SLURRY COATING PROCESS TO MANUFACTURE PBX USING A DESIGN OF EXPERIMENT APPROACH

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The energetic material development team at AWE have developed and optimized the coating efficiency and particle agglomeration rate of an aqueous suspension ('slurry') re-precipitation process. The process formulates energetic moulding powder used for detonator work. The main advantage of a PBX over the neat explosive powder is that, when pressed, the PBX has better mechanical and thermal properties, which is vital for detonator handling. The process has been demonstrated at the 50g scale using live explosives. A 500ml jacketed glass reactor, equipped with a multi-port flange top and an IP-rated high torque mechanical overhead stirrer is used to process the formulation. Proof of concept was initially carried out using inert density mocks of the live material. Calcium carbonate, magnesium carbonate and cyanuric acid were trialled. However, results showed that inert simulants did not agglomerate in the same manner as the live material, primarily due to their dissimilar surface energies.

A wettability study was carried out to determine alternative binder options for the PBX. Binders to be tested included; Kynar ADS, LFC-1, FK-800, Kraton 1650 and OXY-461. A series of experiments was carried out at various binder loadings to evaluate coating efficiency. During the live trials encapsulation and agglomeration was observed. The results showed that the greater the quantity of binder, the better the coating and agglomeration efficiency. The granule size appeared large when in suspension at the end of the process, however when the material was dried, the granules appeared to be reduced in size. This may have indicated that the solid bridges holding granules together were weak. Further analysis showed that partial coating was evident, which is believed to be the reason why a low figure of insensitiveness was recorded (sensitivity of explosive to impact).

A Design of Experiment approach was carried out to determine the factors that would influence the end-product. From this data the process could then be optimised to achieve the desired product consistently. A 3 factor, 2 level, 2 centre point DOE was established as a starting point with the option to augment the design in the future. The three factors to be analysed in the DOE are mixing rate, rate of lacquer addition and cooling duration. A total of 10 experiments, where each of these factors where varied, were thus carried out and responses measured. Examples of responses include bulk and tap density (Hausner ratio), figure of insensitiveness, average coating thickness via XPS and average granule size.

149. ROLLER COMPACTION: MONITORING THE POWDER TEMPERATURE FROM FEEDING TO COMPACTION ZONE.

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In the roller compaction process, the powder is fed towards two counter-rotating rollers and compressed into ribbons. During this process the powder temperature increases due to the compaction and friction. In the previous studies, the temperature of ribbon was monitored after releasing between the rollers, which is less than the temperature of the powder in the compaction zone [1-3]. It is very important to know the temperature in the feeding zone and how it increases while powder moves towards the compaction zone. The temperature at this stage plays a vital role especially for the amorphous materials which help identify the state of material (glassy or rubbery state), by comparing this temperature to the glass transition temperature of the powder (Tg).

A new method was developed to monitor the temperature of the powder in the feeding and compaction zone in the roller compactor - Alexanderwerk WP120. In the compaction zone, the stress applied on the powder, and the compact density starts to increase gradually and reaches its maximum at the minimum gap between the roller. Powder temperature changes with the varying positions from feeding to compaction zone. In addition, amorphous and crystals materials behave differently with the increase of stress from the rollers. The temperature distribution has been recorded in different regions while the powder is being fed to the compaction zone.

[1] C.S. Omar, R.M. Dhenge, J.D. Osborne, T.O. Althaus, S. Palzer, M.J. Hounslow, A.D. Salman, Roller compaction: Effect of morphology and amorphous content of lactose powder on product quality, Int J Pharm, 496 (2015) 63-74.

[2] M. Yu, C. Omar, A. Schmidt, J.D. Litster, A.D. Salman, Improving feeding powder distribution to the compaction zone in the roller compaction, Eur J Pharm Biopharm, 128 (2018) 57-68.

[3] J.D. Osborne, T. Althaus, L. Forny, G. Niederreiter, S. Palzer, M.J. Hounslow, A.D. Salman, Investigating the influence of moisture content and pressure on the bonding mechanisms during roller compaction of an amorphous material, Chemical Engineering Science, 86 (2013) 61-69.

150. GROWTH AND INTERNAL MICROSTURCTURE OF GRANULES FROM WETTING AND NON-WETTING POWDER BLENDS

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Recent work in granulation has provided insight into the rate processes controlling granulation, however much of this research has been conducted using hydrophilic powders and water based binders. Pharmaceutical wet granulation commonly involves the granulation of mixtures of non-wetting powders (often API) and wetting powders (usually excipients). These systems are known to experience some problems with content uniformity within a granulation batch [1]. On the other hand, poor wettability can also result in granules of unique microstructure- hollow granules- that can improve compactability of granules and dissolution kinetics of tablets [2]. Some studies have observed the formation of liquid marbles, with the bulk of research focused on nucleation and on the formation of liquid marbles in such systems (e.g. [3]). These researchers have made strides to answer the question "Why are liquid marbles formed?" However, little is known of the subsequent granule growth and the resultant granule microstructure, and this provides the motivation for this study.

In this work various blends of non-wetting micron-size pharmaceutical powder (Efavirenz) and wetting excipient (red iron oxide) were granulated using dextran solutions of differing viscosities in both tumbling drum and high shear granulators. Granule microstructure and composition were characterized using XRCT and SEM/EDS. The effect of blend wettability, granulation time and binder viscosity on granule microstructure and size were investigated.

Granule size was found to increase with increasing binder viscosity and mixing time, and decrease with contact angle. Granule coalescence was increased at lower binder viscosity and prolonged mixing time. Higher binder viscosity gave rise to poor liquid distribution and reduced the deformability of the granules. The thickness of the liquid layer at the surface of these granules was shown to be reduced. It is hypothesised that this is because less liquid is squeezed to the surface during collisions, resulting in slow agglomerate growth [4].

Hollow granules were obtained in both hydrophobic and hydrophilic blends across a range of conditions, with intra-granule void space promoted by high binder viscosity, low shear forces, and low mixture wettability. Shell microstructure is complex and highly non-uniform in radial direction. Binder viscosity is shown to play a critical role in granule microstructure.

[1] T.H. Nguyen, W.Shen, K.P. Hapgood, Effect of formulation hydrophobicity on drug distribution in wet granulation, Chemical Engineering Journal, 164 (2010) 330–339.

[2] K.P. Hapgood, L. Farber, J.N. Michaels, Agglomeration of hydrophobic powders via solid spreading nucleation, Powder Technology, 188 (2009) 248–254.

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[4] T. Schæfer, C. Mathiesen, Melt pelletization in a high shear mixer. VIII. Effects of binder viscosity, International Journal of Pharmaceutics, 139 (1996) 125–138.

151. EFFECT OF TPGS ON DISSOLUTION SENSITIVITY OF A POORLY-WATER SOLUBLE DRUG USING HIGH-SHEAR WET GRANULATION

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2 Department of Pharmaceutical Commercialization Technology, Merck & Co., Inc. West Point, PA, 19486, USA
3 Department of Analytical Sciences, Merck & Co., Inc., West Point, PA, 19486, USA
4 Department of Biopharmaceutics, Merck & Co., Inc., West Point, PA, 19486, USA
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Surfactants have been widely used as a means to enhance dissolution, solubility, and/or bioavailability of poorly-water soluble drugs. However, the incorporation of surfactants especially d-α-Tocopheryl polyethylene glycol 1000 succinate (TPGS) in tablets can be challenging in terms of undesirable effects on compaction, physical stability, and processing. Therefore, the goal of this study is to demonstrate the potential application of high-shear wet granulation (HSWG) as a way to effectively incorporate surfactants such as TPGS for improving the product performance. Specifically, TPGS-containing HSWG formulations could potentially minimize achlorhydric effects typically existing in patients co-administered with proton pump inhibitors (PPI) or H_2 receptor blockers.

In this study, amorphous drug A, a poorly water-soluble drug with very fine particles, and crystalline drug B, highly water-soluble drug, were concurrently incorporated in HSWG formulations with the spraying of TPGS solutions to enhance the dissolution, apparent solubility, and bioperformance of drug A. TPGS levels were also optimized and defined based on dissolution, bioperformance, physical stability, and tablet properties. The wet granulated formulations had significantly improved processing and flow properties. TPGS-containing HSWG formulations outperformed roller compacted formulations in dissolution and bioperformance under achlorhydric conditions. The formulation robustness of the HSWG formulations was also demonstrated since the dissolution profiles of drug A following HSWG were similar in spite of different drug A attributes. Therefore, HSWG formulations with the addition of TPGS can be used as a means to minimize not only the achlorhydric effects but also the sensitivity of dissolution against variable drug A attributes.

152. MODELLING THE PENDULAR, FUNICULAR AND CAPILLARY STATES BETWEEN SPHERICAL PARTICLES

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Capillary forces play a significant role in wet granulation processes since they are responsible for the forces of attraction between the primary particles to form agglomerates. Numerical solutions based on the Fast Multipole Boundary Element Method (FMBEM) for 3 and 4 spherical particles with inviscid liquid bridges are presented and compared with previously published experimental data for a system based on glass beads and water; a schematic diagram for the case of 4 particles is shown in the Figure. Furthermore, the critical separation distances are computed at which the transitions from the capillary, funicular and pendular states occur. The calculated capillary forces are consistent with the publish measured values. The FMBEM calculations showed that gravitational distortion of the liquid junctions is important for the higher liquid contents.

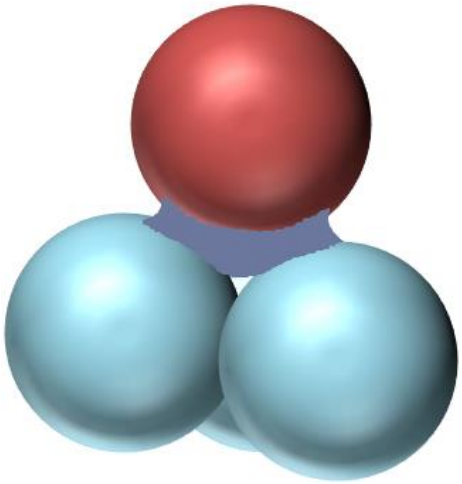

Figure 1. Schematic of four particles with interstitial liquid

153. ADVERSE EFFECTS OF PLASTIC NANOPATICLES IN SOIL ENVIRONMENTS

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Environmental distribution and adverse effects of plastic debris on biota is of significant concern. Although studies on plastic pollution in the soil media are quite limited in comparison to that in other media such as sea water and fresh water, important achievements have been made, and these can be used to promote further research. Furthermore, the organisms considered in existing studies are very limited and may not be representative of real conditions, but the findings can be applied to future studies considering more organisms. Examples from marine and freshwater studies can be applied to expand the scope of future studies on plastic pollution in soil. This study suggests new perspectives to promote and expand studies of plastic debris in the soil media. In addition, we provide important topics the will help researchers expand the study of plastic pollution, thereby reiterating the seriousness of plastic pollution in soil.

154. EVALUATION OF BIOMASS GRANULES AS ADSROBENTS FOR REMOVAL OF HEAVY METALS AND DYES

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The main objective of this research was to transform anaerobic digestate material into a value added product. Biomass granules for use as adsorbent for removal of heavy metals and dyes was produced from drum granulation process. In this research anaerobic digested was used as raw material in the production of biomass granules using drum granulation technique. Aqueous solution of odium silicate was used as the binding fluid. The effect of sodium concentration in the solutions on the granule attributes was investigated. The results obtained showed that the concentration of sodium silicate used had positive influence on the mechanical strength of the granules, increasing the concentration increases the strength of the granules. However, increasing the concentration has a negative influence on the adsorption properties of the granules. Methylene blue and chromium solutions were used as model adsorbates for dyes and metals respectively. The influence of the sodium silicate composition on removal efficiency varies depending on the adsorbate; for chromium increasing concentration has a negative effect on removal efficiency whilst it for the dye presence of silicate enhances the removal.

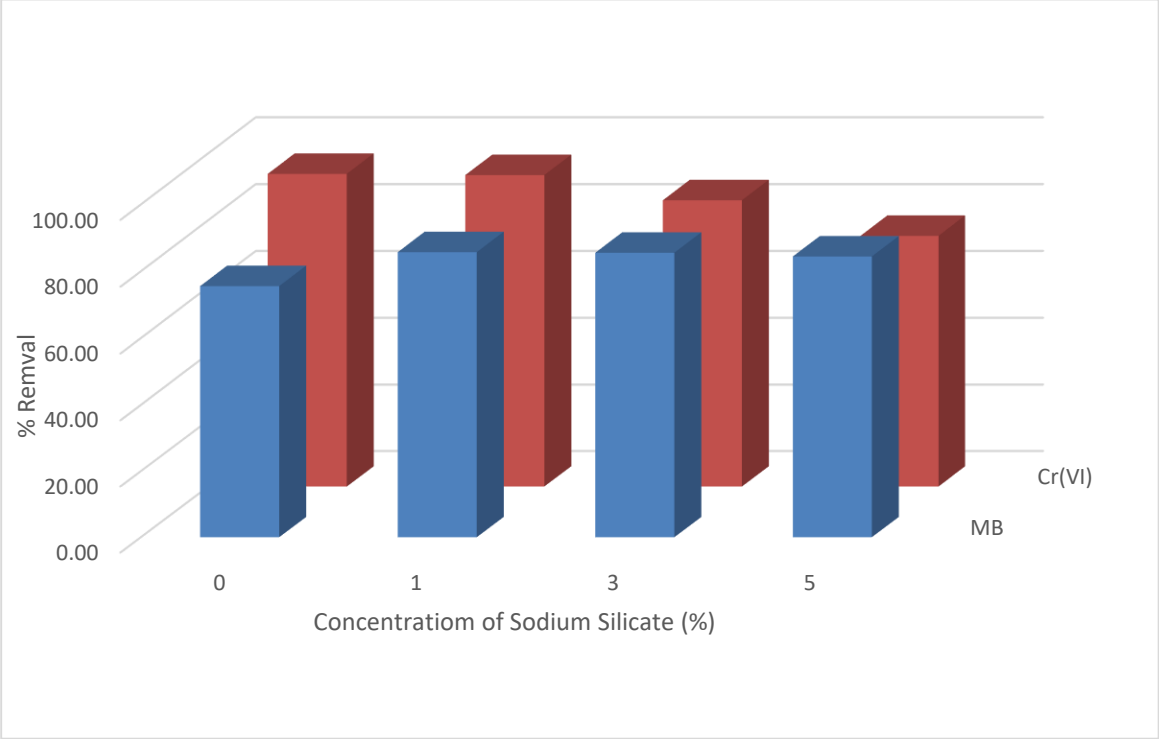

Figure 1. Effect of sodium silicate binder concentration of removal efficiency of methylene blue and chromium (IV)

[1] Y. Yang, Z. Wei, X. Zhang, X. Chen, D. Yue, Q. Yin, et al., Biochar from Alternanthera philoxeroides could remove Pb(II) efficiently, Bioresource Technology. 171 (2014) 227–232.

155. CAKING BEHAVIOUR OF LACTOSE DUE TO SOLID-STATE CRYSTALLIZATION OF AMORPHOUS CONTENT

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This work deals with caking behaviour of lactose monohydrate powders containing small amounts of amorphous lactose. The objective was to elucidate the relation between the caking ability of powder mixtures and the crystallization behaviour of amorphous lactose. Binary mixtures consisting of amorphous lactose and α-lactose monohydrate were prepared and tested using an accelerated caking test. Amorphous lactose samples were prepared using both freeze-drying and spray-drying techniques. Two caking devices were developed to characterize the caking ability of powders. The effect of amorphous content, relative humidity, temperature and pressure on the caking behaviour of samples was investigated. The results showed that the presence of even small amounts of amorphous lactose (as low as 0.125%) could cause caking. The more influencing parameters were found to be the relative humidity and the temperature whereas the pressure has no significant effect. The caking behaviour was shown to be closely linked with crystallization extent and kinetics. A dimensionless time based on Avrami model for crystallisation rate was defined allowing unifying the experimental data.

156. DEVELOPMENT OF DESIGNED SHAPE CALCIUM PHOSPHATE GRANULES

Andris Putnins, Jana Vecstaudza & Janis Locs

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Calcium phosphate (CaP) granules are well known bone fillers. Sufficient bone regeneration is expected for bioceramic granules with inter-granular porosity of 70-80% [1]. Such inter-granular porosity can be achieved by specific design of granule shape. Aim of this study was to develop hollow CaP granules with increased inter-granular porosity.

Granules were prepared by wet granulation by filling paste-like CaP into moulds. Later granules were dried and heat treated at 1100°C. 8 different C shapes and 2 differently sized Y shapes were tested (see figure). Outer diameters of granule moulds were 1.6-2.8 mm. The optimal granule mould shape was selected empirically by evaluation of ratio between number of whole granules after drying and number of filled moulds (*mould efficiency*). Important step in selection of mould shape was to ensure that the granule does not crack throughout the drying process. Addition of polyvinyl alcohol solution to paste-like CaP eliminated granule cracking during drying. In addition, increase of CaP content in the paste reduced cracking as well. Granule sizes after drying were 1.3-2.5 mm and 0.9-1.8 mm after heat treatment. Mould shapes that showed *mould efficiency* over 80% were the C-shaped No 7 and No 9 without curvature on the ends. Inter-granular porosity of such hollow C-shaped CaP granules were around 57±7% in comparison of 43±5 with irregular non-hollow CaP granules.

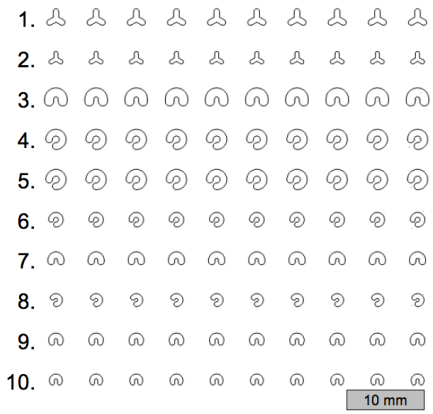

Figure 1. Different shapes and sizes of moulds for formation of CaP granules.

[1] X. Zhang, Q. Cai, H. Liu, B.C. Heng, H. Peng, Y. Song, Z. Yang, X. Deng, Osteoconductive effectiveness of bone graft derived from antler cancellous bone: an experimental study in the rabbit mandible defect model. International Journal of Oral and Maxillofacial Surgery, 41 (2012) 1330-1337.

157. OBTAINING AND CHARACTERIZATION OF C-SHAPED CALCIUM PHOSPHATE GRANULES FOR BIOMEDICAL APPLICATION

Andris Putnins, Jana Vecstaudza & Janis Locs

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Calcium phosphate (CaP) materials are widely used for bone defect filling. There is a need for granular bone fillers with different bulk porosities and bulk densities, that cannot be obtained with conventionally prepared granules by crushing of larger aggregates. Aim of the study was to prepare C-shaped CaP granules and compare with conventionally shaped ones.

CaP was hydroxyapatite that was prepared by precipitation reaction from CaO and H_3PO_4. C-shaped granules were prepared by filling *wet* CaP mass into PTFE moulds, then granules were dried, removed from moulds and sintered at 1100 °C. Bulk density, bulk porosity and shrinkage were determined for C-shaped granules and compared to irregular granules of the same composition prepared by crushing method.

C-shaped granules had smaller bulk density of 0.89±0.02 g/cm^3 and higher bulk porosity of 57±7% than the irregular granules with bulk density of 1.32±0.02 g/cm^3 and bulk porosity of 43±5%. 70% of pores in bulk body of C-shaped granules was in size of 0.2-0.4 mm, that is optimal for bioceramic granules [1]. Interesting feature was observed after firing of single C-shaped granule in heating microscope in different positions (see figure). When fired upright position at 1100 °C the inner angle becomes smaller, while in downright position - the inner angle increases substantially and is responsible for breaking of granules.

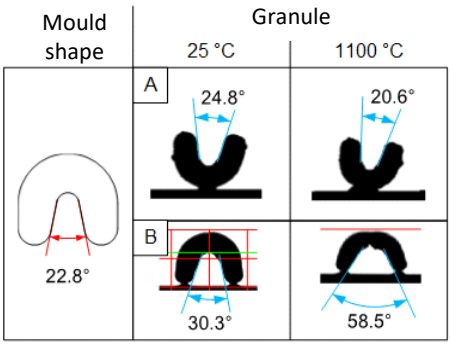

Figure 1. Heating microscopy images of granule inner angle changes after drying (25 °C) and sintering (1100 °C): A - granule in upright position, B - granule in downright position.

[1] X. Zhang, Q. Cai, H. Liu, B.C. Heng, H. Peng, Y. Song, Z. Yang, X. Deng, Osteoconductive effectiveness of bone graft derived from antler cancellous bone: an experimental study in the rabbit mandible defect model. International Journal of Oral and Maxillofacial Surgery, 41 (2012) 1330-1337.

158. INFLUENCE OF MAGNESIUM STEARATE COATING ON CAKING OF PVP

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Povidone (PVP) is widely used in pharmaceutical industry in powder formulations as binder, film former and emulsion stabilizer. It is prone to caking during processing and storage. To avoid excessive powder caking, the effect of magnesium stearate (MgSt) coating on caking of PVP is investigated by Ball Indentation Method.

Blends of MgSt (0.5%, 1%, 2% and 4% w/w) and PVP were processed by two types of mixers, a low-shear Turbula mixer and a high-shear impeller-driven mixer. Extent of coating of MgSt on PVP powder was assessed visually by SEM. Caking experiments were conducted at relative humidity (RH) of 75% at 25 °C and 45 °C. Results show that low-shear Turbula blending at 30 rpm for 10 min has no significant influence on PVP caking compared to untreated sample, implying that low-shear blending provides insufficient energy to distribute MgSt particles effectively over the surfaces of PVP powder. However, high-shear (1000 rpm for 10 min) impeller-driven mixing is shown to have a significant effect on lowering the rate and extent of caking of the PVP powder to the extent that it could even be effectively inhibited with 0.5 wt% MgSt addition at 25°C and 75% RH. However, at the higher temperature of 45°C and the same RH of 75%, a much higher level of MgSt addition (4 wt%) is needed to prevent caking of PVP.

159. RECONSTRUCTION OF BUBBLE SPATIAL DISTRIBUTION IN FLUIDIZED BED

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In bubbling fluidization, bubble spatial distribution, bubble size and bubble rising velocity have primary effect on solid mixing, solid-gas contact, gas residence time, solid dispersion, and heat and mass transfer in chemical reactors [1]. Intensive investigations have been carried out since the 1960s to characterize and predict bubble properties using various techniques, such as bubble size, bubble rise velocity, and bubble spatial distribution. However, most work either focus on 2-D fluidized bed or a section of 3-D fluidized beds. The obtained bubble spatial distribution may not be able to represent the bubble behaviour in the entire bed. In this study, a new approach was developed to reconstruct bubble behaviour and bubble spatial distributions in a 3-D fluidized bed based on solid motion that is measured by the PEPT technique. The bubble size and rise velocity were calculated based on solid velocity in bubble wakes. Bubbles locations in the bed were identified from solid velocity profile. The relationship between solid flow patterns and bubble spatial distribution as well as the specific surface area of bubbles were also evaluated. The bubble spatial distribution reconstructed agreed very well with the solid flow patterns A to D presented in our previous publications [2]. The results and the reconstruction approach were discussed and verified respectively with well-known correlations and published literature.

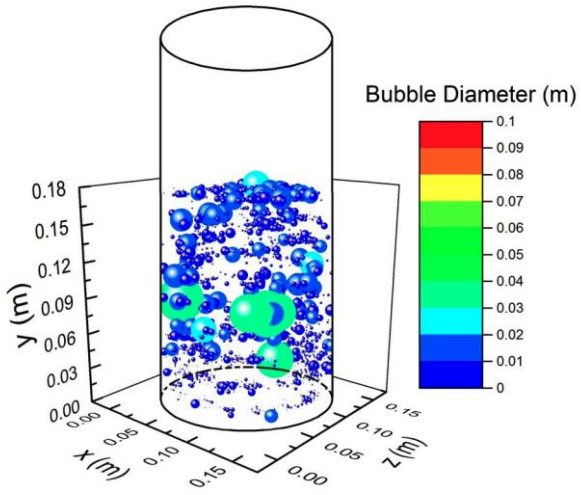

Figure 1. Bubble spatial distribution in a bubbling fluidized bed (Pattern D)

[1] C.N Lim, The dynamics and control of bubbling fluidised beds, University of Bristol, 2004.

[2] Y. Li, H. Fan, X. Fan, Identify of flow patterns in bubbling fluidization, Chemical Engineering Science, 117 (2014) 455-464.

160. DEVELOPMENT OF AGE APPROPRIATE FIXED DOSE COMBINATION MEDICINES AS SPHERONISED GRANULES TO TREAT CHILDHOOD TUBERCULOSIS

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Until recently, there was no appropriate product available to treat tuberculosis (TB) in children. Often unlicensed adult fixed dose combination (FDC) tablets were manipulated, resulting in under or over dosing with unfavourable therapeutic outcomes [1]. The aim of this study was to develop a fixed dose combination product with flexible dosing options containing isoniazid (INZ) and pyrazinamide (PYZ) in the form of coated spheroid granules. The extrusion spherionization technique was used to produce spheroidal granules.

The quality of each formulation was measured via the following parameters: size; aspect ratio (AR); circularity; friability; bulk and tapped density and angle of repose. The yield was greatest for the 65% INZ granules at 77%; a poor yield for 65% PYZ granules (28%) meant that an alternative PYZ formulation with 40% drug loading was manufactured which gave a yield of 38%.

The results showed that INZ and PYZ at 65% drug loading produced larger granules with an average diameter of 1mm and 0.99mm respectively compared to 0.51mm for the PYZ at 40% drug loading. PYZ pellets were more spherical with AR of 1.13±0.06 and 1.18±0.32 for 65% and 40% drug load. INZ had an acceptable AR of 1.12 which is within the spheroid particles range but resembled an oval shape figure (1). The 65% INZ resulted in the strongest pellets with loss during the friability test at 0.4% compared to 1.2 and 1.4% for the 65 and 40% PYZ granules respectively. Stronger granules are more suitable for the coating process. The Hausner ratio, % Carr's index and the bulk density results show a good flowability of the pellets for the three formulations.

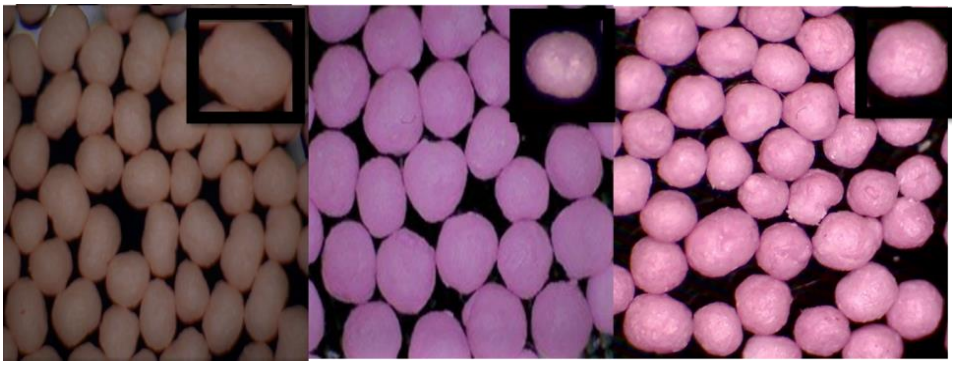

Figure 1. Images of the spheroid granules starting from left to right the 65% INZ,65% PYZ and 43% PYZ (magnification = x15).

[1] Pouplin, T., Phuong, P., Toi, P., Nguyen Pouplin, J. and Farrar, J. (2014). Isoniazid, Pyrazinamide and Rifampicin Content Variation in Split Fixed-Dose Combination Tablets. PLoS ONE, 9(7), p.e102047

161. EFFECT OF SWIRLING FLOW ON PARTICLE BEHAVIOUR IN SUPERSONIC SEPARATORS FOR NATURAL GAS PROCESSING

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The separation of the water vapour and heavy hydrocarbons is an essential procedure in the natural gas processing. The supersonic separation is a newly designed device for this purpose combining the supersonic condensation and cyclone separation, in which the particle flow is one of the key issues to determine the separation performance. The present work presents numerical simulations of the complex particle motion in a supersonic separator with a swirling device located in the entrance of the supersonic nozzle. The effect of the swirling flow on the granulation of the condensed droplets is analysed using the Discrete Particle Method, including the collision, breakup and coalescence. The results show that most particles collide with the walls or entered into the liquid-collection space directly due to the strong swirling flow, while only few particles escape together with the gas flow. The optimisation results present that the separation efficiency reaches 96%, when the vane angle is fixed approximately at 40^o with the height of the vane is about 12.5% of the entrance diameter of the supersonic nozzle.

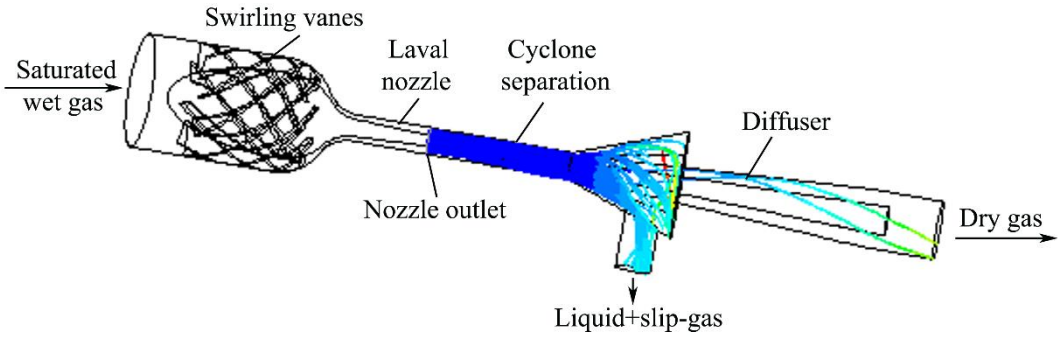

Figure 1. Particle flows in a supersonic separator

162. EXPERIMENTAL STUDIES OF SAND EROSION BEHAVIOUR ON PIPELINE STEEL UNDER DIFFERENT PARTICLE CONCENTRATION AND SIZES

Yan Yang[1, 2], Hongmin Xu[1], Haoping Peng[1], Chuang Wen[3] & Yuqing Feng[4]

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2 Department of Mechanical Engineering, Technical University of Denmark, Nils Koppels Allé, 2800 Kgs. Lyngby, Denmark
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E-mail: yyang@mek.dtu.dk

The internal corrosion of oil and gas pipelines can cause serious accidents, including the leakage and explosion, which not only affects the safe operation of the pipeline system but also emits pollutions to the surrounding environment. The solid particles gathering usually occur in the oil and gas pipelines because of the ups and downs of the landform. The fluid flow can carry the solid particles and result in the erosion corrosion problems on the internal surface of the pipelines, in which the particle agglomeration plays a significant role. In this study, the experimental studies were conducted to investigate the erosion corrosion due to the particle transportation and deposition in the oil and gas pipelines. The results show that the increasing sand concentration induces an increase of the erosion corrosion rate in the initial lower concentration. When the sand concentration is high, too much sand will produce a "shielding effect" on the inner surface of the pipe steel, resulting in the decline of the erosion corrosion rate. The surface of the pipe steel mainly presents the corrosion behaviour in the low sand concentration. On the contrary, the erosion marks are observed on the pipe surface under the conditions of high sand concentration. The increase of the sand size aggravates the erosion corrosion issue of the inner surface of the pipe steel. The maximum mass loss rate of the measured specimen reaches 11.2 g m^{-2} h^{-1}, when the particle size is around 210 μm.

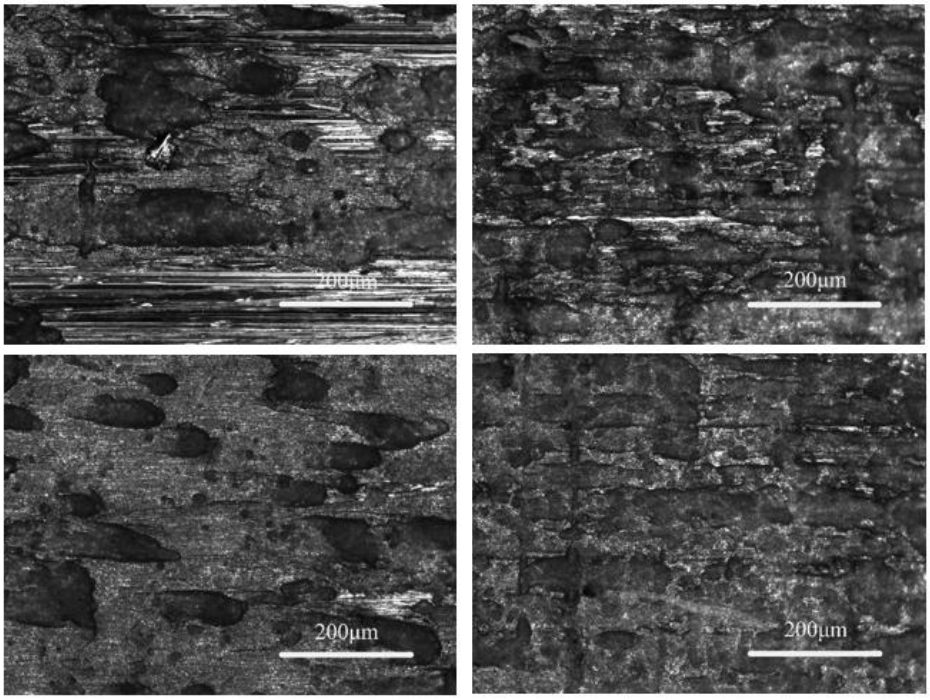

Figure 1. Erosion morphology of pipeline steel under different sand sizes

163. SULPHUR FINISHING PROCESS: PRILLING VS GRANULATION

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The oil and gas industry produce sulphur as a by – product when the feed constitutes of sulphur compounds such as H2S. Sulphur can be removed from sulphur containing compounds via the Claus process and many other processes using sulphur recovery units. Granulation is a method which is key in many industries to manufacture many products and intermediates such as fertilizers, pharmaceuticals and the nuclear industry. The process of granulation involves improving the flow, handling, strength, structure, appearance and many other material properties [1]. As for the process of prilling, the procedure was developed to bring about uniformity and enhance product quality. One of the prilling processes for sulphur involves molten sulphur being pumped into perforated trays and then poured into an agitated water bath dropwise forming sulphur prills due to the interaction with water. This is the wet-prill process [2].

Within this paper, it is aimed to examine two samples of sulphur, one of which in the prilled form and the other in granule form. The two different samples underwent testing for certain mechanical and material properties which were of certain interest. Structure of the prills and granules, size distribution, strength testing and porosity measurements have been analysed after testing. It was found that there are certain irregularities between sulphur prills and granules when looking at size and strength. Other properties related to these two samples will be tested and trends will be analysed to conclude the best process in terms of physical and mechanical properties.

[1] Rahmanian, N., Ghadiri, M., Jia, X. & Stepanek, F. Characterisation of granule structure and strength made in a high shear granulator. Powder Technology , 192(2) (2009) 184-194.

[2] Shamskar, K. R. The effect of quenching temperature on structural and mechanical properties of sulfur prills. Powder Technology, 217(1) (2012) 128-133.

164. TEMPERATURE MEASUREMENT OF FLUIDIZING PARTICLES USING A THERMAL CAMERA

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Fluidized bed is used in many industries for different applications including drying, coating and granulations, due to the favourable mass and heat transfer characteristics. In this process, the temperature of the fluidising particles change with time, which will affect the mass and heat transfer rate. Therefore, an accurate determination of particle temperature during the process is essential.

Thermal camera is recently used to measure temperature of fluidizing particles [1, 2]. This process involves an image processing technique of the recorded thermal images, which requires an accurate selection of the pixels representing particles. In the recent studies [1, 2], the pixels representing the particles were broadly selected by assuming that the temperature of particles are all higher or lower than a threshold, while the movement of particles were not considered.

In this study, it is found that the movement of particles can cause significant measurement errors. Therefore, only pixels that can be accurately represent particle temperature are selected using image processing technique. This was then validated experimentally. It was found that the technique used can significantly reduce the measurement errors caused by particle movement.

[1] A. V. Patil, E.A.J.F. Peters, V.S. Sutkar, N.G. Deen, J.A.M. Kuipers, A study of heat transfer in fluidized beds using an integrated DIA/PIV/IR technique, Chem. Eng. J. 259 (2015) 90–106.

[2] V.S. Sutkar, N.G. Deen, A. V. Patil, V. Salikov, S. Antonyuk, S. Heinrich, J.A.M. Kuipers, CFD-DEM model for coupled heat and mass transfer in a spout fluidized bed with liquid injection, Chem. Eng. J. 288 (2016) 185–197.

165. MODEL ANALYSIS OF THE EFFECT OF MOISTURE ADDITION AND ITS FORM ON INTERPARTICLE FORCE OF THE LIGNITE PULVERIZED COAL

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E-mail: mhzxjinyong@126.com

Coal is the most reliable energy and chemical raw materials in China, and coal-dominated energy structure will not change in 2050. In China, the high-quality coal resources, such as bituminous coal and anthracite, have been fully utilized. The rich reserved lignite is underutilization of capacity, because of its high moisture content and complicated internal interactions. In this paper, lignite samples with different moisture contents were prepared. Shear test and compressibility test were carried out to investigate the influence of moisture content on the flowability of lignite powders. Combined with the thermogravimetry and flowability results, the different moisture content forms and their mathematic models were clearly defined and established. According to these model, the interparticle forces were calculated which were further used to predict tensile strengths. The predictions were compared with those obtained from the shear test, giving errors mostly smaller than ±5%.

166. STUDY ON MULTISCALE STRURCTURE OF FLOW PATTERNS IN DENSE-PHASE PNEUMATIC CONVEYING OF PULVERIZED COAL

Yong Jin, Haifeng Lu, Xiaolei Guo & Xin Gong

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In this paper, fine pulverized coal was used as the experimental materials and a series of conveying experiments were conducted on the dense-phase pneumatic conveying experiment platform in the Key Laboratory of Coal Gasification of Ministry of Education (ECUST, China). Four typical flow patterns, including packed bed flow, plug flow, churn flow and dilute phase flow, were defined and their characteristics were analysed. The high frequency pressure signals were decomposed by the Daubechies second order wavelet transform and analysed by the fractal analysis. A clearly defined classification of microscale, mesoscale, and macroscale signals has been put forward, which represented the particle flow friction, particle-wall interaction and the interaction between gas and solid phase. Furthermore, based on the multiscale structure characteristics of pressure signals, useful features from the particle-related properties derived from multiscale resolution of the high frequency pressure signals, were extracted to establish to predict on-line measurement of flow patterns.

167. COMPARISON OF TENSILE STRENGTH OBTIANED FROM DIFFERENT ASPECTS

Haifeng Lu, Jiakun Cao, Xiaolei Guo, Cong Luo & Xin Gong

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Tensile strength is the maximum amount of tensile stress that powder can take before failure. It is regarded as one of the most important properties of powder and has been paid more and more attention. In this paper, a couple of powders including copper powder, glass beads, coal, alumina powder, petroleum coke and carbon black powder were used as experimental materials. The tensile strengths of different powders were determined based on compressibility test, shear test and fluidization test performed with the standard methods of FT4 Freeman powder rheometer. Comparisons of tensile strength obtained from different respects were carried out. And, effect powder properties on test produces as well as on tensile strength were analysed as well. These experimental values obtained from different respects were further compared with those predicted from the general formulation derived by Rumpf with the interparticle force expressed by Van der Waals force form to give a better understanding of the significance of the tensile strength.

168. STUDY ON THE AERATED DISCHARGING PROCESS BASED ON A TWO-DIMENSIONAL HOPPER

Xiaolei Guo, Jiming He, Haifeng Lu & Xin Gong

Key Laboratory of Coal Gasification and Energy Chemical Engineering of Ministry of Education, Shanghai Engineering Research Center of Coal Gasification East China University of Science and Technology, Shanghai 200237, PR China
E-mail: gxl@ecust.edu.cn

In this paper, based on the background of aerated hopper in the powder feeding system，the high-speed camera system was used to study the bubble motion characteristics and the effects of aerated discharging in a two-dimensional hopper. The experimental results show that the hopper discharging has an important influence on the bubble movement in comparison to that of no discharge. During the aerated discharging process, some of the bubbles will move down with the particles and run out of the hopper, and because of the particle motion in the middle flow region, the lateral velocity of the bubble decreases and the bubble lateral displacement is smaller. The particle flow region is influenced significantly by the bubble movement during the discharging process. Under the different aeration conditions, the flow region of the particles is positively correlated with the discharging rate, and both of them increase with the increase of the aeration gas velocity until a constant value. As for the aeration position, whether the single or the combined aeration, the higher the location of aeration is, the smaller the flow region in the hopper.

169. PREDICTION OF SOLID DISCHARGE RATE OF POWDER DISCHARGED FROM HOPPERS WITH INSERT

Dong Sun, Haifeng Lu, Xiaolei Guo, Jiakun Cao & Xin Gong

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In this paper, lignite and glass bead with different particle size were select as experimental materials, whose flow properties were characterized by FT4 Powder Rheometer and PT-X Powder Tester. The effect of intensification and mechanisms of the insert on the solid discharge rate were analysed and the motion of particle in the confined zone formed by setting the insert was investigated by carrying out discharge experiments on a Perspex silo platform. By modifying the Beverloo equation, a formula to predict the solid discharge rate of powders discharged from the hopper with an insert is developed. Effects of powder properties on its flow behaviours was analysed quantitatively and a detailed outline about physical characteristic was determined. Experimental results show that the introduction of the insert is beneficial to powder discharge and compared to glass bead, the discharge rate of lignite with poor flowability achieves a larger increase of 58%.

170. STUDY ON POWDER DISCHARGE FROM HOPPER WITH AN INSERT

Haifeng Lu, Jiakun Cao, Dong Sun, Xiaolei Guo, Xueli Chen & Xin Gong

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This paper mainly focuses on the study of powder feeding system with the background of pressurized entrained-flow gasification technology of pulverized coal. Because pulverized coal has poor flowability and is hard to discharge from hoppers, the intensification of the flow process is studied. Pulverized coal with strong adhesiveness was selected as the research material and the discharge experiments were carried out in the self-built transparent Perspex silo with an aerated insert. The influence of silo insert on the discharge rate was investigated, and the mechanism of the particle flow in the confined region formed by the silo insert was analysed. From the point of gas-solid fluid dynamics, as a way to intensify the process, the effects of the aerated insert on the discharge rate of pulverized coal and the flow pattern of the particles at the outlet were discussed. Finally, the characteristics, development and evolution of flow zone under the action of aerated insert were explored.

171. A NOVEL SOLVENT FREE HIGH SHEAR TECHNIQUE FOR PREPARATION OF SPHERICAL PHARMACEUTICAL COCRYSTALS

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Cocrystals, are solid dosage forms having two different molecules in the crystal structure, both of which interact by hydrogen bonding or any other non-covalent bonds and solid at ambient conditions of temperature and pressure. Pharmaceutical Cocrystallisation is used to modify several physicochemical and mechanical properties of active pharmaceutical ingredients (APIs), including stability, dissolution rate and bioavailability without affecting their pharmacological activity [1].

In this work we are proposing a high shear melt granulation (HSMG) as a novel technique for cocrystal formation, whereby low melting point polymers are used to assist cocrystals formation in spherical shapes granules under high shear mechanical force. Equimolar ratio of Salicylic acid (SAL), Nicotinamide (NIC) was granulated with Polyethylene glycol 4000 (PEG4K) 15% w/w, inside a GMX-Lab micro top blade high shear granulator for 60 min. It was found that HSMG is a versatile solvent free technique for cocrystals formation with advanced physiochemical and mechanical properties,

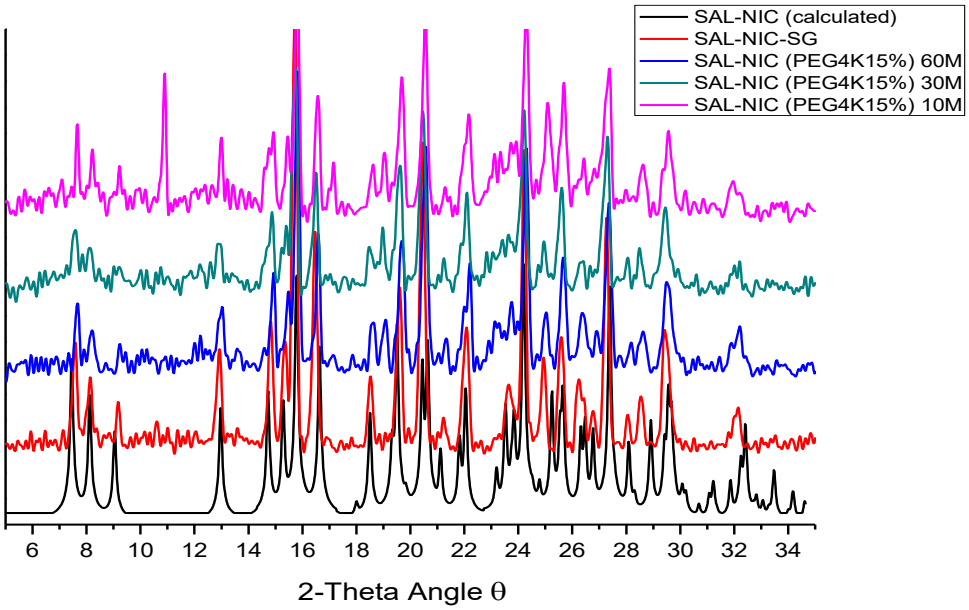

Figure 1. PXRD of calculated SAL-NIC, solvent assistant and HSMG samples at three different time intervals.

[1] P. Barmpalexis, A. Karagianni, I. Nikolakakis and K. Kachrimanis, European Journal of Pharmaceutics and Biopharmaceutics, 131 (2018) 130-140.

172. MICRO-ENCAPSULATION OF LACTOFERRIN USING PROTEIN-TANNIC ACID MULTILAYERS TARGETING LOWER GASTROINTESTINAL TRACT

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Functional food with integrated bioactive compounds have a potentially positive effect on health and beyond basic nutrition means. Lactoferrin (Lf) is a globular protein widely used in food, cosmetic and pharmaceutical applications as it exhibits a variety of beneficial biological activities with safety and biocompatibility properties. One of the major challenge associated with optimizing the performance of Lf is its rapid degradation by proteolytic enzymes found in gastrointestinal tract. In this work, we propose the use of novel encapsulation materials for the protection of lactoferrin to target lower gastrointestinal tract [1, 2]. The fabrication of Lf-based oral delivery systems as shown in Figure 1 will be highlighted and the performance based on loading and protection efficiency will be discussed.

Figure 1: Scheme of Lactoferrin (Lf) encapsulation using post-loading of Lf in porous $CaCO_3$ microparticles followed by Layer-by-Layer deposition of protein and tannic acid and final dissolution of $CaCO_3$.

[1] Kilic, E., Novoselova, M.V., Lim, S.H., Pyataev, N.A., Pinyaev, S.I., Kulikov, O.A., Sindeeva, O.A., Mayorova, O.A., Murney, R., Antipina, M.N. and Haigh, B., "Formulation for Oral Delivery of Lactoferrin Based on Bovine Serum Albumin and Tannic Acid Multilayer Microcapsules", Scientific Reports, 44159 (2017) 7.

[2] Lau, H.H., Murney, R., Yakovlev, N.L., Novoselova, M.V., Lim, S.H., Roy, N., Singh, H., Sukhorukov, G.B., Haigh, B. and Kiryukhin, M.V., "Protein-Tannic Acid Multilayer Films: a Multifunctional Material for Microencapsulation of Food-derived Bioactives", Journal of Colloid and Interface Science, 332 (2017) 505.

173. EXPERIMENTAL STUDY ON THE EFFECT OF METAL PROTRUSIONS INSIDE SILOS ON ELECTROSTATIC DISCHARGES

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This paper experimentally introduces the electrostatic discharges generated from metal protrusions inside a silo during the loading of powders. An industrial-scale pneumatic powder transport facility including a silo (Figure 1), and approximately 400 kg of polypropylene powder (PP, 2-3 mm in size) was used for this test. The PP powder loading speed was about 0.38 kg/s. Six different diameters (1 cm to 6.3 cm) of metal protrusions were used. The metal protrusions were attached to the silo wall using a 30 cm support rod and was electrical grounded. The height from the accumulated PP powder in the silo varied from 10 cm to 50 cm. During the test, the level of PP powders accumulated inside the silo was constant because the PP powders were continuously circulated through the pneumatic transport pipeline. An image-intensifier unit was used in order to observe electrostatic discharges and a current prove attached to an oscilloscope was used to measure the current of discharges. As for the results, electrostatic discharges (such as brush discharges) from protrusions during the loading of PP powders was clearly observed (Figure 2). Especially, electrostatic discharges started clearly spreading from the protrusion when a 3 cm protrusion was used. The frequency of discharge decreased with an increase in the diameter of the protrusions, but the strength of the discharge increased. The discharge duration time increased with an increase in the diameter of the protrusions, and the height did not make a big difference. The maximum charge amount of brush discharges in all of the tests conditions was -229 nC. These results suggest that in the chemical process, powders wetted with solvents, along with the solvents themselves, must be carefully handled as these kinds of powders can be ignited by brush discharges. In order to prevent and reduce electrostatic accidents, it is important to make sure no external material enters the silo.

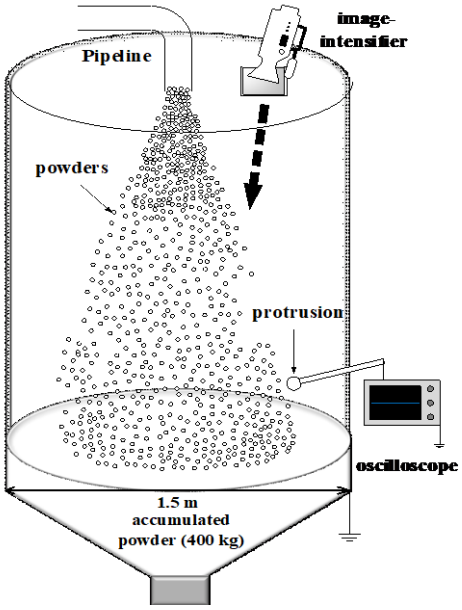

Figure 1: silo used in this study.

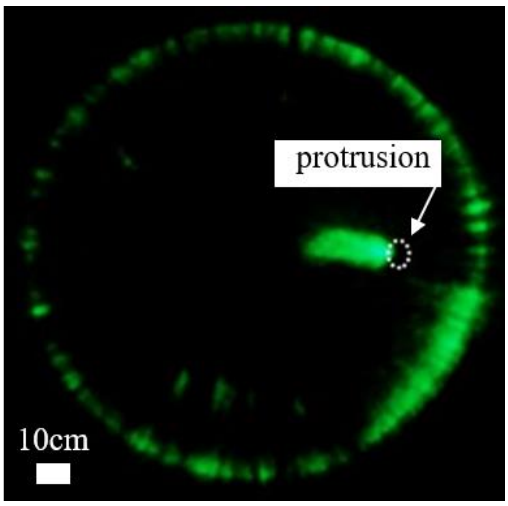

Figure 2: electrostatic discharges from

174. HOW TO ASSESS COHESION OF UNCONSOLIDATED POWDERS AT HIGH FLOW FIELDS?

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Granulation is the most common process of particles enlargement by agglomeration technique. The main purpose is to transform fine powders into free-flowing and dust free products easier to pack and compress. However, several challenges remain in terms of granules quality, content uniformity and physicochemical properties (flowability, packing, bulk density, porosity, …). Nonetheless, few relevant measurements methods are available in the market to answer this need. Indeed, the stress state and the flow field of the powder should be comparable in the measurement cell and in the process. The perfect example is classical rotating blades rheometers (inspired by fluids rheometers) where the presence of the blades will change the porous media properties during measurements.

Finally, the measurement must be fully automatic to avoid any influence of the operator. With these information in mind, we decided to develop a workflow of instruments to answer pharmaceutical industries requirement for granulation process. Our main goal is to have one instrument per geometry that describes accurately and precisely the process, instead of one instrument for every process with a poor accuracy and precision.

In this presentation, we show how modern technologies can yield relevant results to meet current requirements of industries. In particular, we show how classical tests can be automatized and coupled with images acquisition systems or electronic sensors to give reproducible and interpretable results. The tapped density measurement method has been automatized to act as a quality control test. It can measure precisely the bulk density, the tapped density and the packing dynamics of a powder (GranuPack instrument). The flow rates through orifices of different sizes are measured electronically to study powder flowability (GranuFlow instrument) in a vertical flow. The repose angle measurement method has been revisited to measure powder cohesiveness from the heap irregularities (GranuHeap instrument). A dynamic version of the repose angle is measured with a rotating drum (GranuDrum instrument). More fundamentally GranuDrum allows to measure powder Cohesion. However, materials that have the propensity to charge may highlight fluctuating cohesion and hence unstable flow. For this reason, a new instrument able to measure powders triboelectricity (GranuCharge instrument) will be also presented.

In order to illustrate how these measurements methods can be used in practical cases, different types of common powders have been analysed. The obtained results allow showing the influence of grains characteristics (grain size, grain size distribution, grain shape) on the macroscopic powder properties (density, rheology, etc.).

175. GRANULATION APPROACHES TO DEVELOP SOLID DOSAGE FORMULATIONS OF POORLY SOLUBLE COMPOUNDS CONTAINING A LOW MELTING SURFACTANT

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Vitamin E tocopherol polyethylene glycol succinate (TPGS), a nonionic surfactant is known to enhance the bioavailability of poorly soluble drugs by solubility and permeability enhancement. Processibility of TPGS formulations into solid dosage forms is challenging due to the low melting (~37ºC) and waxy nature of TPGS and the energy intensive pharmaceutical unit operations. The objective of this study is to (a) assess the application of an extrusion spheronization (ES) approach towards developing high drug load, high TPGS solid dosage forms [1] wherein the process complications arising from traditional high energy processes are mitigated and (b) explore the feasibility of conventional high shear granulation coupled with unique formulation approaches to develop film coated tablets containing TPGS [2].

For the ES capsule formulation, a high shear wet granulation (HSWG) process in conjunction with an extrusion-spheronization process was used to generate multiparticulates. A 20% w/w aqueous TPGS solution was used as granulating fluid and a target TPGS solid concentration of 10% w/w was achieved with a drug load of 75% w/w. The ES process resulted in multiparticulates with approximately a sphericity factor of 1.2. Most of the energy intensive steps could be circumvented and particle sizing was performed in the wet state. A high drug load of 75% w/w and a TPGS level of 10% w/w could be achieved. Pharmacokinetic performance, evaluated in dogs, was comparable to a 25% DL and 10% TPGS conventional HSWG formulation potentially indicating more intimate API-TPGS contact from the ES process. For the tablet formulation, a 20% w/w solution of vitamin E TPGS was used as granulating fluid and WG formulations with 40% DL were evaluated in a multivariate design. Impact of varying levels of TPGS, HPC (binder) and Prosolv (extragranular filler selected based on a pre-DOE study) was evaluated on response factors such as tensile strength (TS), friability, disintegration and dissolution. The potential impact of temperature elevation during processing was assessed through a heated die fitted onto a compaction simulator, an oven study and a coating study. Bilayer tabletability of the TPGS formulation with another HSWG non-TPGS formulation was also studied. TPGS levels significantly impacted tensile strength, disintegration time and dissolution ($p < 0.01$). Heat sensitivity studies indicated that TS reduction upon exposure to heat was minimized by higher levels of extragranular fillers potentially due to a “shielding effect”. In an oven study, the tablets containing 10%w/w TPGS were physically unchanged after 5 hrs of exposure to 45°C and coating using aqueous dispersions was carried out without any significant processing issues. The interfacial strength of bilayer tablets was acceptable at >1.5 MPa. The study demonstrates feasibility in formulating high drug load/high TPGS formulations by mitigating potential process complications arising from the low melting nature of vitamin E TPGS.

[1] Aditya S Tatavarti and Filippos Kesisoglou. “An Extrusion Spheronization approach to enable a high drug load formulation of a poorly soluble drug with a low melting surfactant” J Pharm Sci. 104 (11) (2015) 3752-3759.

[2] Aditya Tatavarti and Feiyan Jin. "Tabletability Assessment of Conventional Formulations Containing Vitamin E Tocopherol Polyethylene Glycol Succinate" Int J Pharm. 389 (1-2) (2010) 58-65.

176. MODIFICATION OF INDOMETHACIN RLEASE ACROSS ORODISPERSIBLE TABLETES USING PH DEPENDANT POLYMERS

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Introduction: Orodispersible tablets (ODTs) disintegrate in the buccal cavity within few seconds forming a small mass that can be swallowed easily by dysphagia patients. Nonetheless, ODTs are not currently offering a controlled release profiles for medication. This makes it challenging for patients suffering from chronic medical condition as frequent dosing will be required [1]. Aim: to formulate modified release ODTs by using polymeric particulate system with good mechanical properties to maintain the integrity of system during manufacturing and study the effect of particle size on the characteristics of the formulated pellets.

Methodology: Eudragitl100 were sieved in to different particle size powder 45, 63 and 90µm, the mechanical properties of the particles were evaluated using texture analysis and porosometer. Then Eudragitl100 was used to formulate indomethacin pellets using extrusion spheronization technique. The pellets were embedded into tablet matrix to prepare ODTs. Hardness, tensile strength, elasticity profile and aspect ratio were used to characterise the tablets. Results and discussion: SEM images showed that pellets made of 90µm particles were more spherical than other batches;45 and 60µm. The surface area and total pore volume of pellets 45, 63 and 90 µm were 3.26, 4.44, 5.26m^2g^{-1} and 0.007, 0.009, 0.01cm^3 g^{-1} respectively. Pellets prepared of 90µm particles had a significantly large surface area due to high porosity of the pellets. In addition, the 90 µm batch showed high tensile strength of 1.9MPa compared to the rest 0.5 and 0.6 MPa for 45 and 63µm respectively, this was attributed to the rough surfaces of the pellets which provided a high number of binding sites for interparticulate bonds. The drug release profile was prohibited in the acidic media (pH 1.2) for 2 hrs and immediately released in the phosphate buffer media (pH 6.8) for all batches. In addition, the pellets made of 45, 63 and 90 µm had good elasticity profiles 4.5, 4.7 and 4.9MPa respectively. The disintegration time of tablets of pellets of 90 µm batch disintegrated in 14secs while other tablets of pellets of 45 and 63 µm disintegrated in 16secs. Conclusion: the particle size had an impact on the final mechanical properties of the final formulation. Besides, modification of drug release was achieved by using this formulation.

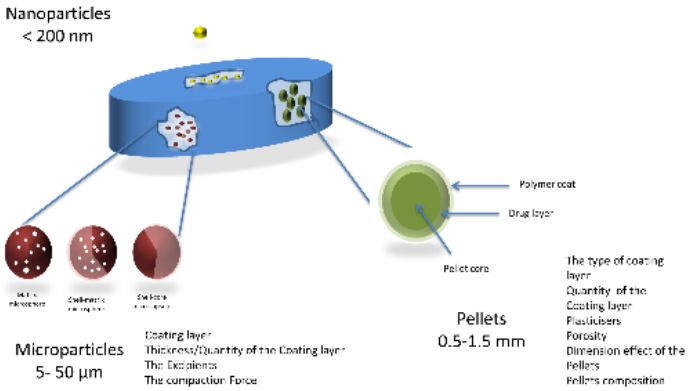

Figure 1: ODTs based on particulate

[1] ElShaer, A., Al-Khattawi, A., Mohammed, A.R., Warzecha, M., Lamprou, D.A. and Hassanin, H. Understanding the compaction behaviour of low-substituted HPC: macro, micro, and nano-metric evaluations. Pharmaceutical development and technology, 23(5) (2018) 442-453.

177. NUMERICAL SIMULATION OF MECHANICAL RESISTANCE OF AGGLOMERATED POWDERS

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This paper presents the results of a study on modelling and numerical simulation of mechanical resistance of agglomerated powders. The numerical simulations were carried out based on Discrete Element Method (DEM). The overall objective of the study was to simulate the behaviour of agglomerated samples subjected to a mechanical, compressive or tractive, stress.

First, simulations were performed on an assembly of particles subjected to capillary forces. Indeed, the capillary forces being amenable to a theoretical description, the tensile strength of wet agglomerates can be calculated theoretically and be used as a reference to validate the numerical simulation results. Thus, the simulation results were validated by comparing them with those obtained by Rumpf's model for a wet agglomerate subjected to a tensile stress. Simulations were based on the combination of conventional DEM method and the phenomenological model of capillary condensation. At each step of time, capillary forces at each binary contact were calculated by assuming that the system is in thermodynamic equilibrium (a_w=RH). The volume of liquid bridges and the extent of capillary forces within a known arrangement of particles at a desired water activity was calculated by the combination of the Kelvin law of capillary condensation and the Laplace law for capillary forces. The stress-strain curves were then simulated and compared to the theoretical values. The results showed a good qualitative agreement between simulation and experimental data.

Once validated, numerical simulations were used to study the mechanical behaviour of wet or dry agglomerates subjected to compression. In order to take into account the cohesive effect of solid bridges at the level of elementary contacts in discrete modelling, we have introduced an Euler-Bernoulli type beam model between particles in contact (Figure 1-a). The stress-strain curves were then simulated and compared to the experimental results. The results showed a good qualitative agreement between simulation and experimental data (Figure 1-b).

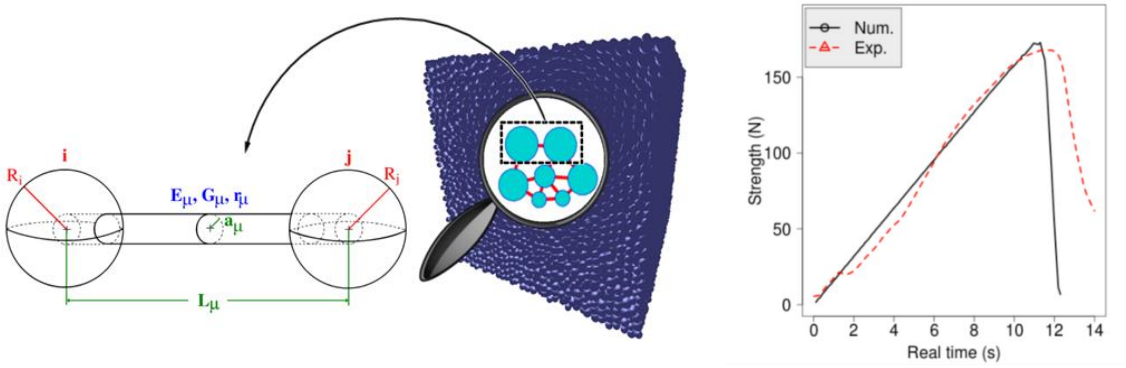

Figure 1. Euler-Bernoulli beam type cohesion model (a) and comparison of simulated and experimental compression curves (b)

178. INFLUENCE OF DRY GRANULATION AND COMPRESSION PROCESS PARAMETERS ON TABLETS' CRITICAL QUALITY ATTRIBUTES - DESIGN OF EXPERIMENTS APPROACH

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Product development or optimization performed in accordance with Quality by Design (QbD) paradigm assumes in-depth understanding of existing relations between process parameters and their output.

The aim of this study was to optimize the process of tablets compression using Quality by Design approach. 3^2 full factorial design was employed to assess the influence of two critical process parameters (CPPs), namely slugging compression force and tableting compression force, on critical quality attributes (CQAs): resistance to crushing, disintegration time and thickness. Mathematical models describing relationships between each of the dependent variables and CPPs were calculated and evaluated. Based on them, 2D contour plot was constructed by overlaying the relationships and taking into consideration the quality specification constraints.

It was found that tablets' resistance to crushing and disintegration time are positively influenced by tableting compression force, and the effect is modified in a nonlinear way by slugging compression force. Tablets' thickness is negatively affected by tableting compression force, while the influence of slugging is negligible. As a result of the research, design space was established to facilitate an in-depth understanding of existing relationship between process parameters and CQAs of the product.

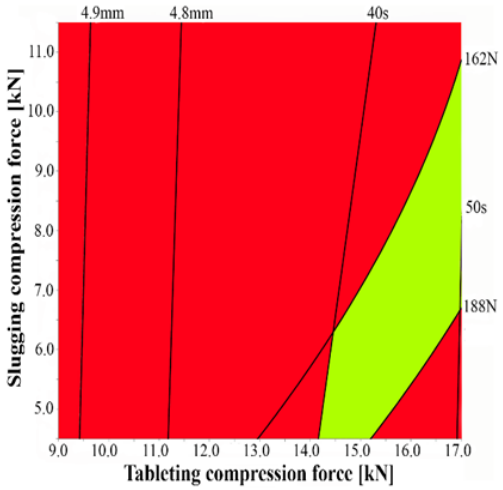

Figure 1: Design Space - an overlaid 2D contour plot presenting the effect of slugging and tableting compression force values on tablets' CQAs [1].

[1] M. Tezyk, E. Jakubowska, B. Milanowski, L Lulek. Implementation of quality by design approach in manufacturing process optimization of dry granulated, immediate release, coated tablets - a case study. Drug Dev Ind Pharm. 43 (10) (2017) 1626-1636.

179. TWIN SCREW GRANULATION: A STUDY OF PRIMARY PARTICLE SIZE EFFECT ON GRANULATION BEHAVIOUR

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In recent years, twin screw granulation (TSG), a wet granulation technique has received great attention from the pharmaceutical industry in order to improve production efficiency and quality assurance. The main advantage of the TSG process is that it can be run continuously, has high flexibility and reproducibility. In literature, many studies have investigated the effect of a range of formulation properties and properties on the resultant granule properties in TSG however the effect of primary particle size has not been sufficiently studied. A few publications that have examined the effect of primary particle size, however, did not maintain the particle shape and morphology; therefore, the understanding obtained on the effect of primary particle size could have been influenced by these two parameters. In the current study, the effect of primary particle size on granulation behaviour and the resultant granule properties was investigated. Experimental investigations were carried out using different screw configurations, screw speeds and liquid to solid ratios. The resultant granule size and structure, an important granule quality attribute for the pharmaceutical industry was then analysed

180. DEVELOPMENT OF GRANULATED BENTONITE FOR POND SEALING

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This paper presents the research focused on the development of granulated bentonite which could be used to decrease the seepage through the dams of very old fish ponds in the Czech Republic of which some are nearly thousand years old. The leakage through the dams can lead to the creation of caverns, preferential flow paths and other defects.

Granulated bentonite is produced of powder Czech calcium magnesium bentonite using the roller press, crushing and sieving. Powder material is named by producer (Keramost Plc.) as Bentonite 75 (B 75). This material has excellent sealing properties in terms of low hydraulic conductivity and was used for the development of new granulated bentonite material. Newly developed granulated bentonite material was named B 75 REC MIX I (Figure left). The development of this material was focused at first on granulation distribution and after that on testing this material with spraying technology. This technology is based on dry process technology for spraying concrete. Figure (right) shows testing of B 75 REC MIX I with spraying technology at testing place of CTU in Prague.

Figure 1: Granulated bentonite B75 REC MIX I in the laboratory (left) and pictures of the spray testing of B75 REC MIX for a sealing layer between concrete walls and soil dam at an experimental model.

Recent results proved that the properties of the developed granulated material is suitable for the purpose of pond dams sealing. For this purpose, low hydraulic conductivity and high swelling pressure are required. The granulated bentonite labelled B75 REC MIX I fulfilled the requirements set out at the beginning of the development.

The research was funded as part of project no. DG16P02M036 the “Conservation, repair and monitoring of historical pond dams as part of our cultural heritage” commissioned by the Ministry of Culture of the Czech Republic. The support is highly appreciated.

181. DEVELOPMENT OF BRAZILIAN ESSENTIAL OILS LOADED GRANULES AND ITS IN VITRO RELEASE STUDY

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One important step on the production of granules consist on its drying, a procedure that influences directly on its microstructural properties such as porosity and shrinkage. Drying involve the removal of the moisture on a solid material through convection, conduction or vacuum, and depending on the substance, such as essential oils, the heating step can be harmful [1-3].

In this work, two drying methods were tested: oven drying, which is a usual technique in many processes involving water losses; and desiccator drying, generally used in sorption isotherms, although in this case it was used as a non-heating drying method. Granules were evaluated by their size range, density, essential oil and water content, in vitro release profile and chromatographic profile of the extracted essential oils. Both granules managed to maintain the initial size between 600-800 μm and essential oil content retention of 45%, however, desiccator-dried granules showed a greater flowability (as observed with a Carr's Index from 2 to 24), less cohesiveness (calculated with Hausner ratio between 1,1 and 1,2) and a lower water content than the oven-dried granules (5% compared with 18%), whilst the oven-dried granules had a higher release profile on in vitro assay, showing a release of 7% of its content, compared to 5% of the desiccator-dried granules. Chromatographic analysis of the extracted oils showed the complete loss of α-pinene (major compound), however, trans-caryophyllene and α-humulene (biologically active compounds) concentrations remained the same, preserving the therapeutic properties in these essential oils.

[1] A. Hegedus, P-H. Klára. Comparison of the effects of different drying techniques on properties of granules and tablets made on a production scale. International Journal of Pharmaceutics, 330 (2007) 99-104.

[2] B. Song, S.L. Rough, D.I. Wilson. Effects of drying technique on extrusion–spheronisation granules and tablet properties. International Journal of Pharmaceutics, 332 (2007) 38-44.

[3] G-C. Ana, C. Souto, M-P. Ramón, A. Concheiro, G-A. L. José. Microstructural and drug release properties of oven-dried and of slowly or fast frozen freeze-dried MCC-Carbopolpellets. European Journal of Pharmaceutics and Biopharmaceutics, 67 (2007) 236–245.

182. PCMM FLUIDISED BED DRYING MODEL FOR CONTINUOUS WET GRANULATION LINE

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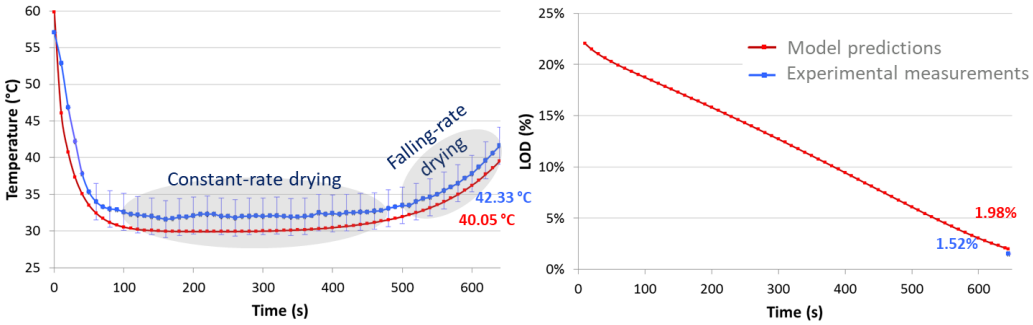
The Fluidised Bed Drying (FBD) process is part of the continuous wet granulation line in PCMM (Portable, Continuous, Miniature and Modular) technology. In clinical and commercial manufacturing this process is carried out in the six-cell dryer ConsiGma-25. It is possible to accelerate process development for new drugs through modelling tools. Specifically, FBD process modelling can help to: scaleup and transfer technology from the one-cell dryer ConsiGma-1 to ConsiGma-25, understand cell-to-cell variability, reduce the number of required experiments for new drugs, and improve the process design for continuous drying. Process simulations allow making better predictions to optimise the drying process and reduce the development time of new compounds. In this work, we have developed a FBD model that captures the most relevant experimental conditions, namely the solid flowrate, amount of liquid added in the granulation, filling time of each cell, and the drying air flowrate, temperature and relative humidity. The model aims at predicting the drying time to achieve granules with moisture content below 2% consistently in all the batches. It is based on material and energy balances, which are related through the drying rate. The model accounts for two differentiated phases, where the free-bound and the close-bound moisture is evaporated respectively; captured through the so-called falling rate kinetics [1]. It has been developed using APAP ConsiGma-25 data with different initial moisture content. Several drying parameters and material properties have been measured using DVS (Dynamic Vapor Sorption) and MAL (Material Assessment Lab) analysis. Other parameters related to the drying rate curve and material transference have been estimated using measured dryer cell temperature and final moisture content from four experiments. Additional experimental data has been used for model validation, using three experiments with same air inlet temperature and flowrate. The FBD model allows predicting the drying curve and drying time for reaching moisture content below 2% for different initial moisture content (Figure 1). It can be directly applied to optimize the drying process using Virtual Design of Experiment and evaluate risk using Global Systems Analysis.



(a) (b)

Figure 1: Comparison of simulated and experimental data of: (a) dryer cell temperature and (b) granulate moisture content.

[1] J. Burgschweiger, E. Tsotsas, Experimental investigation and modelling of continuous fluidized bed drying under steady-state and dynamic conditions, Chemical Engineering Science 57 (24) (2002) 5021-5038.

183. MECHANISTIC MODELING OF FLUID BED GRANULATION PROCESS

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1 Research Center Pharmaceutical Engineering (RCPE) GmbH, Graz, Austria
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Granulation process is adopted in drug manufacturing to achieve desirable granule attributes (e.g., particle size distribution, density and porosity, granule strength, etc.) and the finished product attributes (e.g., content uniformity, dissolution/integration, moisture content, friability, etc.) [1]. The granule enlargement is realized by addition of liquid to the system. Furthermore, aimed at increasing the strength of the granule for further processing e.g., tableting., the particle moisture should be partially removed. Fluid bed granulator is a promising tool to integrate all these features to a single process step. Due to the strong coupling between heat and mass transfer in the fluid bed granulator, developing an affordable tool can be of significant advantage for design and optimization of such process.

In the present work, a mechanistic model was developed to predict the performance of a fluid bed granulator through a flowsheet simulation in gPROMS platform [2]. The developed model accounts for the involved phenomena including i) particle agglomeration, ii) particle drying, and iii) freely-flowing droplet evaporation. In detail, a set of population balance as well as heat- and mass-transfer equations were solved. In addition, the associated model parameters which cannot be readily measured/calculated were estimated for the studied range of operating conditions in the design space.

The detailed analysis of experimental data demonstrated the significant contribution of the degree of wetness in the performance of the bed. It was also observed that the granule final size and loss on drying are inter-related and can be connected via the degree of wetness. Therefore, the associated model parameters associated were mechanistically correlated to the degree of wetness in addition to the other relevant quantities. The reliability of the developed model was evaluated for a new set of operating conditions which was not accounted in the correlation development. In detail, the predicted granule size, loss on drying, and temperature were in a good agreement with the corresponding experimental values. This demonstrated that the developed approach can be used for more efficient design and optimization of FBG process.

[1] R. Gupta, Fluid bed granulation and drying, in: P. Pandey, R. Bharadwaj (Eds.), Predict. Model. Pharm. Unit Oper., Woodhead Publishing, 2017: pp. 137–158.

[2] gSOLIDS® 4.1 Release Notes, (2016). https://www.psenterprise.com/.

184. CORRELATING DRUG-BINDER ADHESIVE STRENGTHS MEASURED USING INVERSE GAS CHROMATOGRAPHY WITH TABLET PERFORMANCE

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The primary particles of pharmaceutical materials often exhibit poor flow and compression behaviour. Granulation can be applied to improve these powder properties. Controlling the adhesive strength between binders and active drugs is paramount in developing successful pharmaceutical formulation. The goal of this study is to predict drug-binder interactions based on the surface energy measurements using iGC-SEA and to correlate results with mechanical properties of the final product [1].

IGC is a well-known tool for the characterization of particles, fibres and films. IGC experiments were carried out using iGC Surface Energy Analyzer (iGC-SEA; Surface Measurement Systems, Alperton, UK) with a flame ionization detector.

Surface energies were measured for model drugs (acetaminophen and ibuprofen) and common binding agents: hydroxypropylcellulose (HPC), polyvinylpyrrolidone (PVP) and hydroxypropyl methylcellulose (HPMC). The surface energy values were used to calculate the adhesive strengths for the various drug-binder combinations, which were subsequently compared with tablet strength data.

The higher the Wadh/Wcoh ratio the higher the tablet hardness and the lower friability. Therefore, higher work of adhesion values (in relation to work of cohesion) lead to stronger tablets. The Wadh/Wcoh ratio is clearly a good measure for the tendency of particles from different materials to interact at their interfaces in comparison to their tendency of sticking together with a particle from the same material. [2]

iGC-SEA surface energy measurements can be used to predict adhesion strengths for different drug-binder systems.

[1] Mukhopadhyay, P., Schreiber, H., Aspects of acid-base interactions and use of inverse gas chromatography, Colloid and Surfaces A, 100 (1995) 47.

[2] Parsons, G E., Buckton, G., Chatman, S M., Comparison of measured wetting behaviour of materials with identical surface energies, presented as particles and plates, Journal of Adhesion Science and Technology, 7 (1993) 95.

185. A STEP TOWARDS PREDICTIVE TABLET TENSILE STRENGTH

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In many powder/ granule compaction processes in industry, the ability to predict the tensile strength of the compact formed prior to any compaction experimentation is generally poor. Therefore an investigation of tabletability-material property of a range of pharmaceutically-relevant materials with different compaction behaviour was performed.

A range of techniques were used to characterise materials before and after granulation and tabletting in order to try and identify correlations between material properties and the tensile strength of tablets produced. Granulation was performed using a twin-screw wet granulator with a range of different screw configurations to change the level of stresses applied. The range of tablet tensile strengths produced using the different materials and different processing conditions was wide. After a thorough investigation it is possible to predict the tabletting behaviour of many materials by measuring few physical properties including the specific surface area. The former property is an important material property upon which a predictive model was build. In the figure below, the specific surface area measured using Brunauer–Emmett–Teller method is plotted against the tablet strength of MCC granules and MCC powder (different particle size) compressed at 44 (MPa). This relationship is the foundation upon which we developed the predictive model.

This is a significant step forward in the ability to predict the tabletting behaviour of materials prior to doing any compaction trials. It also paves the way for the design of next-generation materials with superior compaction properties.

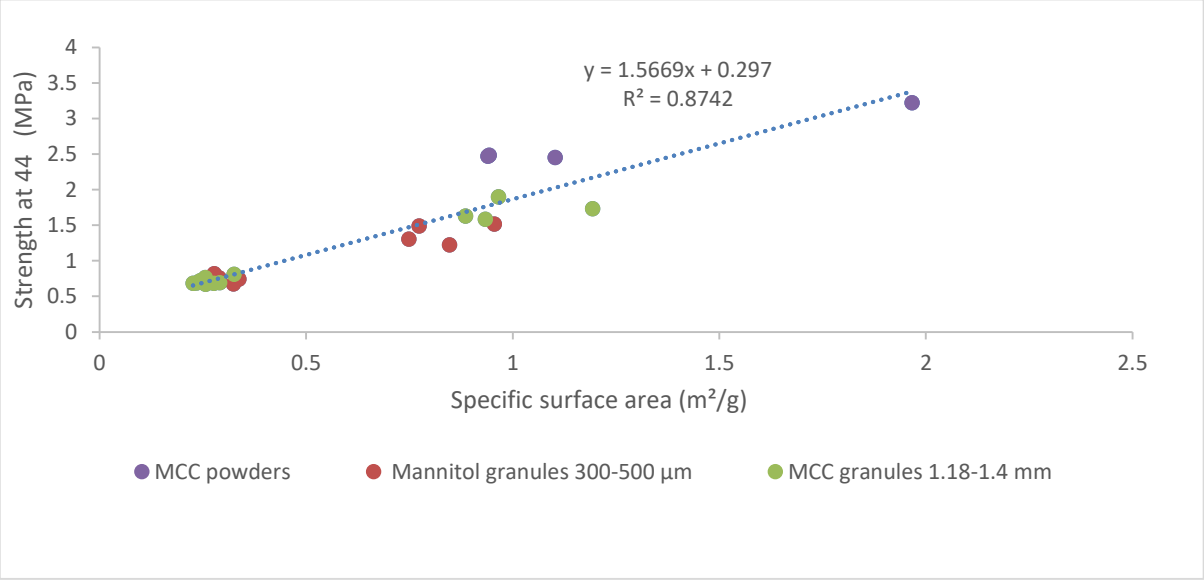

Figure 1 The prediction of tablet tensile strength at a given compaction force based on the specific surface area of the compressed materials.

186. MODELLING THE RECONSTITUTION OF WATER-SOLUBLE POWDERS

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The reconstitution of a powder is a prerequisite for many industries including food, pharmaceutical and detergent. It is therefore important to understand the effect different variables have on the process. Different steps are involved in the reconstitution process including dispersion and dissolution. A mathematical model is developed to describe the reconstitution process and quantify both the dispersion and dissolution steps.

A water-soluble powder, lactose alpha-monohydrate was reconstituted in a mixing vessel under different temperatures (between 20ºC and 60ºC) and agitation speeds (between 600 rpm and 1000 rpm). The vessel was fitted with a Focused Beam Reflectance Measurement (FBRM) probe (Mettler-Toledo) and a refractive index (RI) probe. For each experiment, the concentration of dissolved solids is measured. The curves show an increase in concentration with time; these results are fitted to the mathematical model. The kinetic hypothesis proposed suggests that the dispersion and dispersion steps of the reconstitution follow first order release kinetics. The model showed a good fit with the experimental data and the reconstitution rate is found to improve with both increasing temperature and agitation rates. Additionally, prediction of the dispersed solids fraction is done using the extracted rates and validated using the FBRM.

This approach in addition to tackling disintegration and dissolution can be used to assess how process variables affect the reconstitution behaviour of water-soluble powder

187. CALCIUM CARBONATE SCALE AND AGGREGATION IN OILFIELD: EFFECT OF MAGNESIUM ION AND SCALE INHIBITORS

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Calcium carbonate is one of the most common types of scale that is encountered in various industries. The build-up of scale can negatively affects a wide range of processes including membrane filtration, tubular and heat exchanger causing a frequent replacement of equipment, losses in production and significant charges in service and energy. Various studies have been carried out to study the aggregation and scale formation. In the present study, the influence of magnesium ion and scale inhibitors on the morphology of calcium carbonate aggregated was investigated at wide ranges of temperature. The obtained results in this study were based on microscopic images. It can be concluded from this study that the predominant phase of calcium carbonate at 50^{o}C was calcite. The presence of in-organic minerals in brine solution plays a vital role in scale formation. The presence of magnesium ion can inhibit the calcite growth rate. The reduction in the growth rate is due to the increasing in the solubility of $CaCO_3$ and hence decreasing supersaturation. Scale inhibitors have been a common practice used by many industries to prevent calcium carbonate formation and aggregation for several decades. Chelating effect and lattice deformation are considered the main mechanisms of scale inhibitor.

188. LASER TECHNIQUE TO STUDY CALCIUM CARBONATE SCALE AGGREGATION AND PREVENTION

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Calcium carbonate (CaCO3) scale is one of the most common types of inorganic deposits occurring in industrial water systems, oil and gas production as well as processing operations such as boilers, cooling towers and surface facilities. It may form at different locations due to changes in the water composition or physical conditions such as pressure and temperature. A potential for scale formation is present whenever a solution becomes supersaturated. Scale formation and prevention create a considerable capital, operation and maintenance problem. Achieving effective and economical scale control and removal is consequently a major concern for efficient and safe industrial operations. To prevent such potential problems, it is important to understand the mechanism of the calcium carbonate scaling process.

This paper is part of the continued effort to understand calcium carbonate formation and mitigation related to oilfield operations. The paper describes the application of a new method, based on laser refraction measurement in transferring the signals to current, to determine the formation of calcium carbonate scale in high calcium brines. This method provides a real-time measurement of the magnitude of scaling crystals, and has been proven to be a sensitive method to monitor the initial stages of the precipitation process. This study focuses on the comparison between two techniques to evaluate formation of scale in the presence and absence of scale inhibitors at different temperatures. The study was conducted at 25 and 60°C at different concentrations of CaCO3., and the scale precipitates were characterized using Environmental scanning electron microscopy (ESEM). Also, the efficiency of laser scattering apparatus was assessed as an effective tool for the scale inhibitors performance and ranking, where the results were compared with the offline measurement technique.

189. PAT MONITORING OF COATING PAN BY NIR: PLS METHOD CALIBRATION APPROACH

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The importance of real-time controlling the production processes in pharmaceutical industry is growing, to ensure a precise reproducibility, especially regarding modified release solid dosage forms, and to spare materials, shorten the process time and, consequently save money.

In this study the coating process in pan was taken in consideration, different coating materials were tested, the process was monitored by NIR acquiring a spectrum every 10 seconds and the coating thickness and weight gain were monitored by a micrometer and a digital scale at regular intervals. Data were analyzed using Unscrambler Software

The NIR device proved to be a very versatile and effective process analytical technology to monitor the pharmaceutical prefigure 1cesses. This technology has a very high sensitivity and precision, and it is possible to find a strong correlation between the spectra and different physical variables, this makes the NIR a very valuable device to get an efficient process control. In particular, the response of the software was very reproducible from batch to batch and almost identical to the measured data both in terms of weight gain and coating thickness

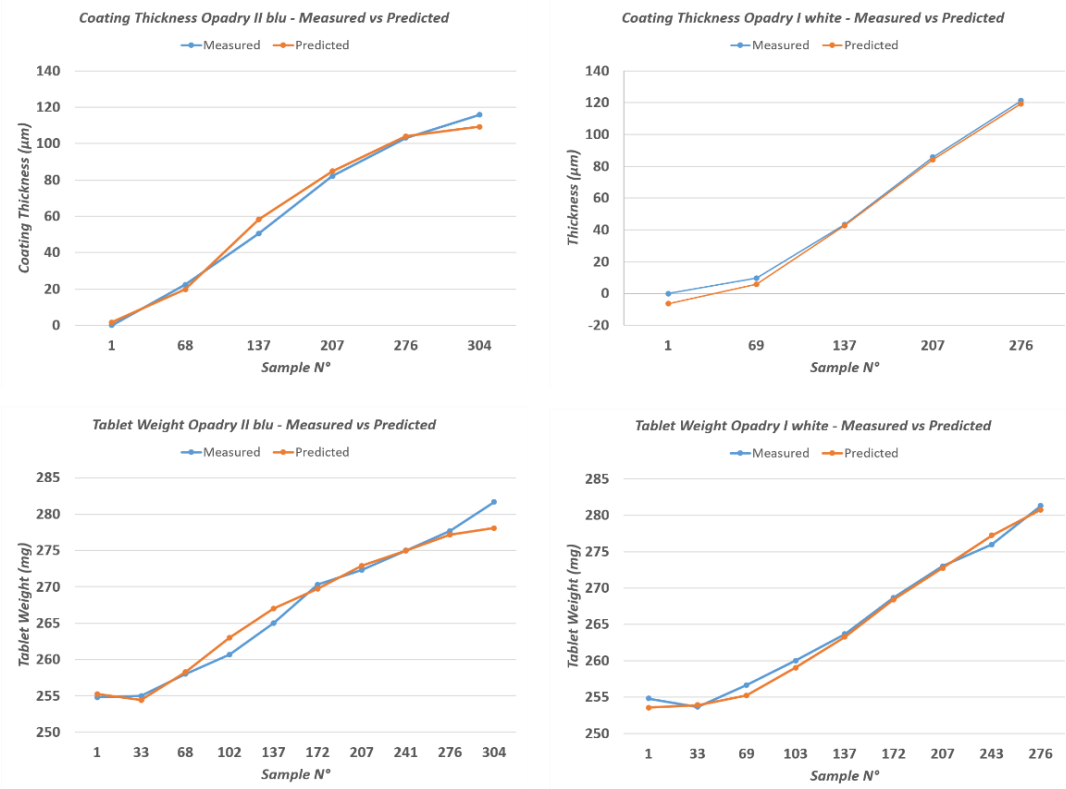

Figure 1: Measured vs Predicted values comparison

190. DRYING IN A CONTINUOUS WET GRANULATION LINE: INVESTIGATION OF DIFFERENT END OF DRYING CONTROL METHODS

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Continuous manufacturing in the pharmaceutical industry has been gaining traction in the past few years. To fully understand and optimise continuous manufacturing processes it is important not only to focus on the single units which act as building blocks but is also essential to understand how the parameters in different units affect and interact each other and the final product.

In this study the drying behaviour, of granules produced in a twin screw granulator, in a segmented fluidised bed dryer which is part of a continuous powder to table line (Consigma-25) was investigated utilising the temperature readings during the drying process of granules produced with different amounts of liquid binder. Two methods available in the equipment to control the length of the drying processes were also investigated, both using a constant time approach and a target temperature approach. From the temperature profiles, it was possible to create a method able to detect the end of the drying process and therefore predict the optimal drying time at different conditions. The method was validated via online NIR measurements to detect the moisture content of the granules during the drying. The drying rate was also calculated making it possible to predict the optimal drying time at different operating conditions in the granulator.

191. CONTINUOUS MANUFACTURING IN THE PHARMACEUTICAL INDUSTRY：REVIEW OF DIFFERENT SIMULATION METHODS

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Continuous granulation has received an increasing attention nowadays. In order to understand the complicated behaviour of the powder and the granule during the manufacturing process, modelling techniques have been developed and received much attention due to their possibility to minimise large scale physical trials. Different simulation approaches have been applied such as physical based models and data driven models. Physical based models, e.g., Discrete Element Method (DEM), Population Balance Model (PBM) and Computational Fluid Dynamics (CFD), present a deep insight of granulation process whereas data driven models have the ability to predict the granule properties accurately. Due to the systematic simulation result, in pharmaceutical industry, a hybrid model combining physical based and data driven models may be the advisable method for continuous manufacturing simulation in the future. DEM is an approach using equations of motion in all three coordinate directions to analyse individual particle. Hence it is ideal for visualisation of hidden regions and assessing the degree of mixing or segregation along the process. Population balance model (PBM) describes the particle population evolution. It is modelling of a system composed of continuous or discrete number of effects interacting with their environment. CFD, which is a well-established tool normally includes Navier–Stokes solvers with turbulence model, is usually used in pharmaceutical unit operations that involve fluid and multiphase (fluid and solid) systems. Data driven modelling approaches have been utilized to model the granulation process through the recent advanced computing power. The main aim of the data driven approach is to model the granulation processes by mapping the process inputs to the outputs which could represent different granule properties. In this study, different simulation methods of continuous granulation for Consigma 25 line will be evaluated and compared.

192. CONTINUOUS MANUFACTURING OF PHARMACEUTICAL TABLETS: EFFECTS OF PROCESS PARAMETERS IN A TWIN-SCREW GRANULATOR IN CONSIGMA™-25 LINE

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Twin-screw granulation (TSG) is a popular continuous wet granulation technology, where the yield is largely influenced by the process parameters in the granulator. This study focuses on investigating the effect of the process parameters in the continuous line ConsiGma™-25, in particular, screw speed, powder feed rate and stagger angle at specific L/S ratio. The barrel fill level was kept constant when investigating the effect of powder feed rate. The effect of the process parameters on granule size and torque values was evaluated. Finally, the effect on the tablet tensile strength was analysed. It was observed that by maintaining a constant barrel fill level, the granule properties and tablet tensile strength show minimal variation. Varying stagger angle had the most significant impact on the final tablet tensile strength. The output rate of the granules from the TSG was significantly influenced by the stagger angle and powder feed rate. This revealed a significant interaction between the process parameters in the twin-screw granulator and downstream equipment including the fluid bed dryer. The study signifies the need of effective integration of the TSG unit with the fluid bed dryer to minimize the variation on the final tablet properties, which has not been reported before.

193. RECONSTITUTION ANALYSIS OF MILK POWDERS USING A MODIFIED STANDARD METHOD APPROACHING CONSUMER BEHAVIOUR

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The aim of this study was to investigate powder reconstitution using a method that better imitates the real-life reconstitution process compared to standard setups. For this purpose, a custom-made automatic rotating spoon was built, and the results were compared to these obtained using an axial 3-blade impeller. Whole milk and skim milk powder were used as model materials. The properties measured were powder sinking and dissolution time using video recordings during powder reconstitution, coupled with electrical conductivity measurements. The videos were further analysed using Particle Image Velocimetry (PIV) in order to assess the flow pattern and velocity of particles during reconstitution at different conditions. It was found that the rotating spoon led to significantly faster reconstitution than the 3-blade impeller at low speeds; the 3-blade impeller had to operate at speeds between 400 – 700 rpm to achieve the same sinking and dissolution rates as the rotating spoon at 80 – 180 rpm. The results of the present study provide the basis for enhanced reconstitution studies in the future.

194. THE PLASTIC DEFORMATION OF A SINGLE PARTICLE BEFORE AND AFTER ROLLER COMMPACTION PROCESS

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Reducing the tabletability is one of the reported problems of the granules produced by the roller compactor. One of the main possible reasons is the work of hardening that could happen during the roller compaction which reduces the plastic deformation of the ribbon and consequently the granules compared to primary powder. This study determines the nano-indentation hardness of the primary single particle before and after the compaction by the two rotating roller during the roller compaction process at different roller forces.

Three different materials used in the study. Namely, micro crystalline cellulose, lactose and calcium carbonate. These materials represent plastically deformable, partially deformable and brittle material respectively.

195. THE LIMITATIONS OF NIR-CHEMICAL IMAGING FOR DETERMINATION THE TABLET MOISTURE CONTENT

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Determination of moisture content is important for many industrial sectors. It is used to ensure achieving the required quality of the final product. This paper aims at investigating the validity of using a non –destructive near infrared (NIR) chemical imaging (CI) technique as a tool to determine the moisture content of tablet. This technique enables visualizing the spatial distribution of moisture content, as well as providing a quantitative information of the tablet moisture content. Although, this technique enables fast assessment of moisture content, it is associated with some limitations that should be considered when using this technique for such application. This study attempts at highlighting these limitations such as the effect of surface roughness of the sample on the reliability of the NIR-CI result. In this study the effects of tableting compression forces and moisture content on tablet surface roughness and hence its impact on NIR-CI was investigated.

196. PREDICTION OF TABLET TENSILE STRENGTH USING ARTIFICIAL NEURAL NETWORK

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The artificial neural network (ANN) is a powerful tool that can capture complex patterns and highly nonlinear input/output relationships in an available data set that was collected from an examined process. Therefore, an ANN has been used in several areas of science, such as chemical analysis and powder technology. Recently, ANN has been used in the field of processing powders, granules, and tablets. This work aims to build and validate a fast, robust and accurate ANN which can be used to predict the quality attributes tablets.

It has been shown that the ANN with two hidden layers has accurately predicted the tablet tensile strength based on granule and powder properties for 49 batches that have a wide range of mechanical properties. Several material properties were used as inputs for the ANN, including the plastic and elastic work. The performance of the utilised network is presented in Figure 1. The coefficient of determination values for training and testing sets are 0.96 and 0.99.

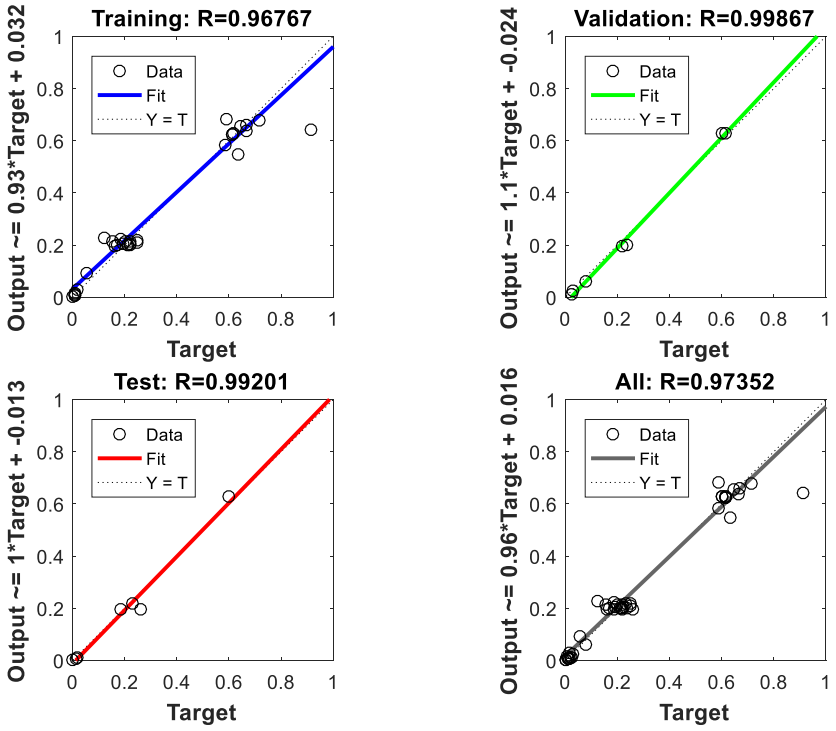

Figure 1. The performance of the artificial neural network based on two hidden layers for the tablets tensile strength as an output and granule properties as inputs.

197. EFFECT OF RIBBON PROPERTIES ON GRANULE SIZE REDUCTION IN DRY GRANULATION PROCESS

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Dry granulation through roll compaction followed by milling is a widely used pharmaceutical process. The material properties of powders and roll compaction conditions affect the strength of ribbons, and subsequently the granule size distribution. Accurate prediction of granule size distribution from milling of ribbons with different properties is essential for ensuring tablet quality in the final compaction stage. In this study, MCC, PH-102 ribbons with precisely controlled porosities and thickness were produced in a die. The ribbons were then milled with both a cutting mill and a conical mill and the granule size distribution were measured by Qicpic. A population balance model (PBM) with a newly developed breakage function was also used to model the granule size reduction. Experimental results showed that the granule size distribution is bi-modal and the amount of fines produced increased linearly with the ribbon porosity. For ribbons with the same porosity value, thicker ribbons lead to more fines in the milling product, which may be caused by the increased chance of attrition/ shear in the mill. The PBM with the newly developed breakage function can precisely capture the amount of fines in the product and can predict the effect of ribbon porosity on granule size reduction very well. The findings from this study have great potential for quality by design of dry granulation process.