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202	Electrostatics effect on bed pressure fluctuation during fluidization of pharmaceutical particles	Lucimara Benelli, Claudia R.F. Souza & Wanderley P. Oliveira	Laboratory of R&D on Pharmaceutical Process, LAPROFAR, University of São Paulo, Faculty of Pharmaceutical Sciences of Ribeirão Preto, Ribeirão Preto, SP, Brazil	Poster	Click here
204	Optimizing the properties of blend for hard gelatin capsules filling by incorporating roller compaction in manufacturing process	Diana Majerová [1], Martina Bartáková[1], Daniela Hofmanová[1], Tomáš Rysl[2], František Štěpánek[1] & Petr Zámostný[1]	1 Department of Organic Technology, Institute of Chemical Technology, Technická 5, Prague, 160 00, Czech Republic 2 Zentiva k.s. (a Sanofi company), U Kabelovny 130, Prague, 110 00, Czech Republic	Poster paper	Click here
205	Roller compaction/ comparison of ribbon and granule properties using different types of lactose	Chalak S. Omar[1], James D. Osborne[1], Tim Althaus [2], Stefan Palzer[2], Michael J. Hounslow[1] & Agba D. Salman[1]	1 Department of Chemical and Biological Engineering, University of Sheffield, Mappin Street, Sheffield S1 3JD, UK 2 Nestle´ Product Technology Centre York, HaxbyRoad,York YO911XY, UK	Poster	Click here

206	In-line measurement of the agglomerate size distribution in fluidized bed agglomeration	Carlos Aviles-Aviles[1,2,3], Michel Terray[4], Elisabeth Dumoulin[1,2,3] & Christelle Turchiuli[1,2,3]	1 AgroParisTech, UMR 1145 Ingénierie Procédés Aliments, 1 Avenue des Olympiades, F- 91300, Massy 2 INRA, UMR1145 Ingénierie Procédés Aliments, F- 91300, Massy 3 CNAM, UMR1145 Ingénierie Procédés Aliments, F- 91300, Massy 4 Malvern Instruments SA, 30 Rue Jean Rostand, F- 91893, Orsay Cedex	Poster	Click here
208	Effect of process parameters during high-shear granulation on the content uniformity of resulting low dose tablets	Sarah Kindgen[1], Marcus Knoell[2], Uwe Schmidt[2], Joshua Müller[2] & Peter Langguth[1]	1 Department of Pharmaceutical Technology and Biopharmaceutics, Johannes Gutenberg-University of Mainz, Germany 2 Hüttlin GmbH – A Bosch Packing Technology Company, Schopfheim, Germany	Poster	Click here
209	DEM investigation of horizontal high shear mixer flow behaviour and implications for scale-up	Ei L. Chan[1,2], Kimiaki Washino[1,2], Jinsheng Fu[2], Hossein Ahmadian[2], Andrew Bayly[3], Michael J. Hounslow[1] & Agba D. Salman[1]	1 Department of Chemical and Biological Engineering, University of Sheffield, Mappin Street, Sheffield, S1 3JD, UK 2 Procter & Gamble Newcastle Innovation Centre, Whitley Road, Longbenton, Newcastle Upon Tyne, NE12 9BZ, UK 3 Procter & Gamble Beijing Innovation Centre, 35 Yu'an Road B Zone, Shunyi District, Beijing, 101312, China	Oral	Click here

210	A quality by design approach to investigate the effect of mannitol and dicalcium phosphate qualities on roll compaction	Nabil Souihi[1, 2], Melanie Dumarey[1], Håkan Wikström[3], Pirjo Tajarobi[3], Magnus Fransson[3], Olof Svensson[3], Mats Josefson[3] & Johan Trygg[1]	1 Computational Life Science Cluster (CLiC), Department of Chemistry, Umeå University, Sweden 2 Industrial Doctoral School, Umeå University, Umeå, Sweden 3 Pharmaceutical Development, AstraZeneca R&D Mölndal, Sweden	Poster	Click here
211	Design space estimation of the roller compaction process	Nabil Souihi[1,2], Mats Josefson[3], Pirjo Tajarobi[3], Bindhu Gururajan[3] & Johan Trygg[1]	1 Computational Life Science Cluster (CLiC), Department of Chemistry, Umeå University, Sweden 2 Industrial Doctoral School, Umeå University, Umeå, Sweden 3 Pharmaceutical Development, AstraZeneca R&D Mölndal, Sweden	Poster	Click here
212	Assessment of single particle contact mechanisms and cohesion under controlled temperature and humidity	Christine I. Haider[1], Tim O. Althaus[2], Gerhard Niederreiter[3], Stefan Palzer[3], Michael J. Hounslow[1] & Agba D. Salman[1]	1 Department of Chemical and Biological Engineering, University of Sheffield, Mappin Street, Sheffield, S1 3JD, UK 2 Nestlé Product Technology Centre, Haxby Road, York, YO31 8FZ, UK 3 Nestlé SA Headquarters, Avenue Nestlé 55, CH-1800 Vevey, Switzerland	Poster	Click here
213	A comparison of granule properties between impeller slash in high shear mixer and screw rotation in twin screw extruder	Zhiyu Wang, Michael J. Hounslow & Agba D. Salman	Department of Chemical and Biological Engineering, University of Sheffield, Mappin Street, Sheffield, S13JD, UK	Poster	Click here

214	Movement of secondary immiscible liquid into a suspension of hydrophilic particles in a continuous hydrophobic phase	Syed F. Islam[1], Steve Whitehouse[2], Ramana Sundara[2], Tim O. Althaus[2], Stefan Palzer[3], Michael J. Hounslow[1] & Agba D. Salman[1]	1 Department of Chemical and Biological Engineering, University of Sheffield, Sheffield, S1 3JD, UK 2 Nestlé Product Technology Centre, Haxby Road, York, YO31 8TA, UK 3 Nestlé SA Headquarters, Avenue Nestlé 55, CH-1800 Vevey, Switzerland	Poster	Click here
215	Glass transition temperature effects on the breakage and dissolution of single amorphous food particles	W. Robert Mitchell, Christine I. Haider, Busayo Onasile, Michael J. Hounslow & Agba D. Salman	Department of Chemical and Biological Engineering, University of Sheffield, S1 3JD, Sheffield, UK	Poster paper	Click here
216	Assessment of granule parameters for implementation in process monitoring and control of twin screw wet granulation using high speed imaging	Arwa S. El Hagrasy[1], Paul Cruise[2], Ian Jones[2] & James D. Litster[1,3]	1 School of Chemical Engineering, Purdue University, West Lafayette, IN 47907 USA 2 Innopharma Labs, Q House Building, Furze Road, Sandyford, D18, Ireland 3 Department of Industrial and Physical Pharmacy, Purdue University, West Lafayette, IN 47907	Poster	Click here
217	Twin screw granulator: Effect of primary particle size	Riyadh B. Al-Asady, Michael J. Hounslow & Agba D. Salman	Department of Chemical and Biological Engineering, University of Sheffield, Mappin Street, Sheffield, S1 3JD, UK	Poster paper	Click here

218	Microscale study of particle agglomeration in fat-based food suspensions: The effect of binding liquid	Alessandra A. Negreiros[1], Tim O. Althaus[2], Gerhard Niederreiter[3], Stefan Palzer[3], Michael J. Hounslow[1] & Agba D. Salman[1]	1 Department of Chemical & Biological Engineering, University of Sheffield, Mappin Street, Sir Robert Hadfield Building, S1 3JD, Sheffield, United Kingdom 2 Nestlé Product Technology Centre, Haxby Road, YO91 1XY, York, United Kingdom 3 Nestlé S.A. Headquarters, Avenue Nestlé 55, 1800 Vevey, Switzerland	Oral	Click here
219	Agglomeration of particles in oil-continuos suspensions driven by liquid bridges	Alessandra A. Negreiros[1], Tim O. Althaus[2], Gerhard Niederreiter[3], Stefan Palzer[3], Michael J. Hounslow[1] & Agba D. Salman[1]	1 Department of Chemical & Biological Engineering, University of Sheffield, Mappin Street, Sir Robert Hadfield Building, S1 3JD, Sheffield, United Kingdom 2 Nestlé Product Technology Centre, Haxby Road, YO91 1XY, York, United Kingdom 3 Nestlé S.A. Headquarters, Avenue Nestlé 55, 1800 Vevey, Switzerland	Poster	Click here
220	Evaluating the solid surface free energy of amorphous maltodextrin	Menan Balashanmugam, Christine I Haider, Mike J Hounslow & Agba D Salman	Department of Chemical and Biological Engineering, University of Sheffield, Mappin Street, Sheffield S1 3JD, UK	Poster paper	Click here
221	Semi-solid binder dispersion in detergent agglomeration	Menan Balashanmugam[1], Andrew E. Bayly[2], Yuen Sin Cheong[2], Micheal J. Hounslow[1] & Agba D. Salman[1]	1 Department of Chemical and Biological Engineering, University of Sheffield, Mappin Street, Sheffield, S1 3JD, UK 2 Procter and Gamble, Beijing Innovation Centre, No 35, Yu'an Road, Tianzhu Konggang Development Zone B, Beijing 101312, China	Poster	Click here

2. UNDERSTANDING EFFECTS OF AIR PRESSURE IN FINE POWDERS DURING ROLL COMPACTION PROCESS

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Roll compaction process is routinely employed in various industrial processes including pharmaceutical and mineral industries. In pharmaceutical industry, the process is used for dry granulation agglomeration of powders to improve flow ability for direct compression, whereas in mineral industry, the process is suitable for fine grinding of mineral materials with an energy-efficient solution. In both previous applications, the process is based on the transport of powders using a screw feeder or rougher gravitational feeding. The powder is then drawn between two counter-rotating rolls in the stressing zone where a high pressure is applied. The common problem encountered in the both applications is related to the non-regular feed rate of powders between rolls, which is commonly attributed to the trapped air into the fine powders. The trapped air leads, in some cases to partial fluidization [1,2] that causes disturbance of the supply powders, noticeable changes of mechanical properties such as ribbon strength and process instabilities.

In the present study, we explore, by modeling, the role of the air transport in the feed powder during the rolling process through the analysis of gas pressure distributions. The model is based on the well-known Johanson model for the solid phase [3], for the prediction of the solid behaviour whereas the fluid transport is assumed to obey to Darcy's law, where the permeability is taken as a function of both material density and particle size through Kozeny-Carman relationship.

From results of the solid properties, gas pressure distribution and process parameters we compare their tendencies to the general findings reported in the literature for the processability of fine powders by roller compaction [4,5]. We also discuss conditions for the escape of air through the porous material during the process according to material and process parameters, especially rolling speed and powder permeability.

[1] J.R. Johanson and A.W. Kenike, The effect of Gaseous Phase on Pressures in a cylindrical Silo, Powder Technology, 5 (1971) 133-145

[2] P.G. Murfitt, P.L. Bransby, Deaeration of powders in hoppers, Powder Technology, 27 (1980) 149-162

[3] Johanson J.R., A rolling theory for granular solids, 1965, ASME, Journal of applied mechanics, 32, n°4

[4] Johanson J.R. and Cox B.D., 1989, Fluid entrainment effects in roll press compaction, Powder handling and processing, vol. 1, n°2

[5] Dec R.T., 1995, Problems with processing of fine powders in roll press, 24rd Biennial Conference of the Institute for Briquetting and Agglomeration, Vol.24, pp.199-210.

3. DEM SIMULATION OF CONTACT INTERACTIONS OF MICROMETER-SIZED PARTICLES

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During the processing sequence, transportation and handling, bulk solids are exposed to a lot of time-dependent mechanical stress due to particle-particle and particle-apparatus contact interactions. Particle behaviour during such interactions can be studied either experimentally or by numerical simulation. The mechanical interactions of particle-wall and particle-particle systems can be well described theoretically with different contact models on the assumptions that a particle has a regular shape. As a matter of fact, the industrial used bulk solids consist of irregular shaped particles. To simulate the real behaviour of bulk materials, the multi-sphere approach can be used.

A particle tester designed to study the mechanical properties of particles in the micrometer regime under cyclic stress was developed at the Environmental Campus Birkenfeld. Recorded data for all loading modes includes force, deformation and 3D shape of the samples before, during and after tests. All experiments were carried out under controlled climatic conditions. Besides TiO2 and alpha-alumina, irregular and spherical maltodextrin particles (in the size range of 50-100 µm) were tested. Based on the experimental data, parameters for contact models for each material were calculated and the experiments were reproduced in a discrete element method (DEM) program. To further study the influence of the particle shape for irregular particles, additional simulations were carried out with the help of the finite element analysis (FEM) under the assumption that materials of tested particles are isotropic and homogeneous.

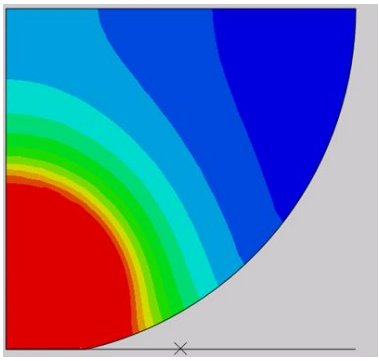

Figure: Axially symmetric FEM model of a spherical particle under compression: distribution of von Mises stress.

Acknowledgements

We gratefully acknowledge for the financial support Deutsche Forschungsgemeinschaft (DFG), Germany. Project number HE 4526/7-2.

4. COALESCENSE MODELS FOR INDUCTION GROWTH BEHAVIOR IN HIGH SHEAR GRANULATION

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High-shear granulation is a favorable size enlargement process in many industries because of its ability to produce small, dense granules and its ability to distribute viscous binder. Heterogeneous powder flow in any high shear geometry from impellers and choppers results in a wide distribution of type and intensity of granule impacts. Multiple granule properties (size, density, liquid content) affect the behavior of the granulation and thus more than one dimension of a population balance should be used to model granulation rate processes.

While the coalescence and consolidation are directly coupled phenomena in the Induction Growth Regime, most PBMs to date define the consolidation rate expression as a simple experimentally fitted model. We hypothesize that these phenomena can be correctly predicted using the 3D PB framework. In this paper, the coupled coalescence and consolidation of granules is modeled using a 3D volume-based population balance framework. The 3D PBM for a horizontal axis high-shear granulator is solved with a two-tier hierarchical solution strategy developed by Immanuel and Doyle [2]. The rate of consolidation, layered growth, and the length of the induction time are predicted as a function of liquid/solid ratio, formulation dynamic yield stress and process conditions. Model predictions are compared to experimental studies in a 5L horizontal axis high shear granulator. Measurements of the liquid binder content, size, porosity and morphology are used to verify rate process mechanisms by varying granulation time, L/S ratio and operating speed. Seeded granulation experiments with well-characterized seed granules are conducted to separate the effects of nucleation and liquid distribution on the growth behavior. These results compared to model predictions for the system show that current rate process models that decouple coalescence and consolidation are of limited scope. Directions for improvements in current modeling strategies are discussed.

[2] Immanuel, C. and Doyle, F. (2005). Solution technique for a multi-dimensional population balance model describing granulation processes. Powder Technology 156, 213–225.

7. THE IMPACT OF DELIQUESCENCE LOWERING ON THE CAKING OF POWDER MIXTURES

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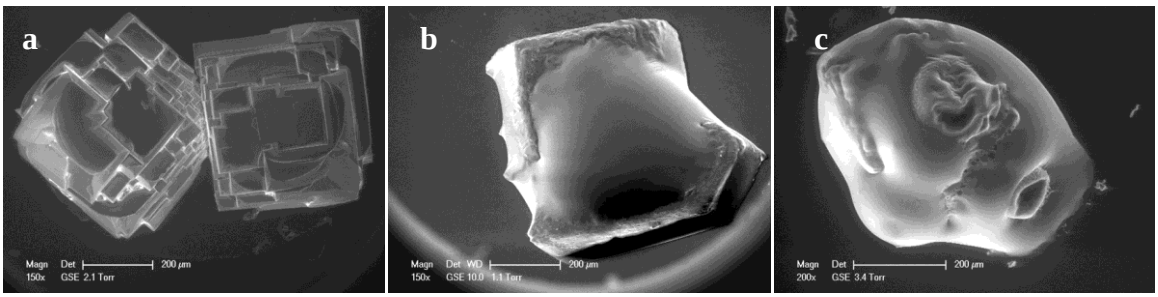
The first step in caking of hygroscopic powders is usually the condensation of water vapour causing deliquescence of solid particles. If water evaporation follows (induced, for example, by the change of ambient conditions) the phenomenon of efflorescence will lead to the formation of solid bridges between particles. Deliquescence takes place at the so called deliquescence relative humidity (DRH) which corresponds to the vapour pressure of saturated solution of the substance. When two or more deliquescent substances are present, a singular behaviour known as "deliquescence lowering" (relating to the mutual deliquescence relative humidity, MDRH), is observed. It was shown that the lowering of deliquescence point favours powder caking [1].

In this study we investigate the impact of deliquescence lowering on the powder stability and its flowability. Binary blend of NaCl and sucrose was chosen as a model system.

Deliquescence lowering of mixtures of NaCl and sucrose was evidenced by ESEM observations and by the quantitative analysis of water uptake. It was shown that the water evaporation leads to efflorescence but also to the formation of an amorphous material. Caking tests, coupled with kinetic measurements of water uptake and loss, are carried out in order to relate the residual water content to the reinforcement of caking of the mixture. The influence of the proportion of two substances in a blend is also analyzed thanks to X-ray diffraction and mechanical tests of tensile strength. It was found that the most sensitive composition with respect to caking is close to the one of the eutonic point i.e. the mixture showing the lowest critical RH at a given temperature.

This work shows that the presence of two (or more) solutes can clearly be more damaging to the mechanical properties and to the stability of powders compared to the situation when only one deliquescent substance is present. The determination of the eutonic composition allows anticipating the conditions under which the caking will be reinforced.



ESEM images obtained after drying, subsequent to partial dissolution of two crystals (a) of NaCl, (b) of sucrose and (c) of NaCl and sucrose

[1] A.K. Salameh, L.S. Taylor, Deliquescence-Induced Caking in Binary Powder Blends, Pharmaceutical Development and Technology, 11 (2006), 453-464.

12. EXPERIMENTAL AND NUMERICAL INVESTIGATION ON THE COMPRESSION BEHAVIOUR OF TETRAHEDRAL AGGLOMERATES

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Institute of Process Engineering, Mechanical Process Engineering, Otto-von-Guericke University Magdeburg, Universitätsplatz 2, 39106 Magdeburg, Germany

The discrete element method (DEM), developed by Cundall and Strack [1] in 1979 to solve geomechanical problems, is applied to simulate tetrahedral agglomerates. By DEM, individual agglomerates can be modelled as a realistic mechanical system consisting of primary particles which are bonded by various interaction forces.

Tetrahedral agglomerates consisting of four primary particles have been selected as model material. The macroscopic agglomerates shown in Figure 1 have been produced using a pelletizing pan. For this purpose, macroscopic dominant elastic-plastic γ-Al_2O_3-granules (d = 1.0, 1.8 mm) have been selected as primary particles. The industrially produced granules are hygroscopic and used as adsorbent, catalyser and desiccant due to their large specific surface. The mechanical properties of the primary particles regarding compression, impact and breakage behaviour have been studied earlier and published elsewhere [2]. As binder different solutions of HPMC (hydroxypropyl methyl cellulose) have been added.

To investigate the mechanical material behaviour of the produced tetrahedral agglomerates at compression, a strength tester has been used, at which the compression test of single agglomerates is performed between two pistons at a constant loading velocity of v = 0.02 mm/s.

At the simulation, modelled tetrahedral agglomerates have been generated. The properties of the primary particles have been set equal to determined properties of γ-Al_2O_3-granules. Diametrical compression has been simulated using two rigid walls between the modelled agglomerate is stressed until breakage. As a result of loading, a force pattern is generated inside the agglomerate.

The force-displacement curves of the modelled agglomerates at compression have been compared to the experimental curve of investigated agglomerates. Moreover, the evolutions of internal tensile and shear stresses within the solid bridge bonds have been recorded. The breakage behaviour and crack propagation have been analysed and compared to the experimental ones. Furthermore, the influence of the primary particle size and the properties of the solid bridge bonds have been investigated.

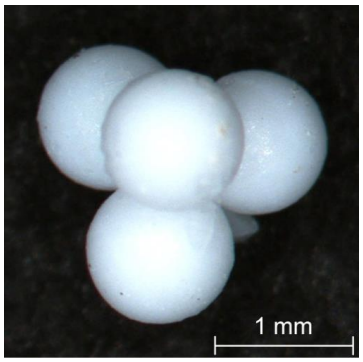

Figure 1: Digital image of a tetrahedral agglomerate

[1] P. A. Cundall, O. D. L. Strack, A discrete numerical model for granular assemblies, Géotechnique 29 (1979), 47-65

[2] P. Müller, Druck-, Stoß- und Bruchverhalten feuchter kugelförmiger Granulate, Dissertation, O.-v.-G.-Universität Magdeburg, docupoint Verlag, Barleben 2011

13. INVESTIGATION ON THE COMPRESSION AND IMPACT BEHAVIOUR OF GRANULES

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During processing and transportation, granules are stressed by compression, impact, friction and attrition e.g. in fluidized beds and at pneumatic conveying. As a consequence, breakage and/or abrasion can be generated in dependence on the stressing intensity. The physical product properties are deteriorated too and the resultant product quality decreases. Therefore, the knowledge of mechanical properties of granules is of vital importance.

Often granules are processed at different moisture contents such as adding liquid binder to the primary feed particles in order to achieve binding, to plasticise the contacts of the primary particles or to achieve capillary rise into the internal pores. As a consequence of wetting and drying the mechanical properties of granules can be changed. Moisture can dissolve existing solid bridge bonds like crystallization bonds or the binding agents. Thus, the strength of the granules can decrease.

At first, the compression of moist spherical granules has been investigated. Two different types of granules have been selected as model granules: γ-Al_2O_3 and zeolite 4A. The granules are industrially produced, easily to handle and are used for different purposes, e.g. as adsorbent or catalyst.

At compressions tests, the moisture content has been found to be an important parameter. With increasing moisture content the material behaviour changes significantly. The γ-Al_2O_3 granules exhibit a decreasing slope of the force-displacement curve and an increasing displacement. In the case of zeolite 4A granules, the force-displacement curve flattens also sharply, however, the deformation remains relatively constant.

At further evaluations, the specific breakage energy distributions and the energetic equivalent breakage velocity distributions have been determined from the force-displacement curves. The strain energy of the granules until breakage is computed with the kinetic breakage energy at impact on a rigid wall. The equivalent breakage velocity corresponds to the impact velocity, at which primary breakage would occur.

Next, the granules have been studied by use of a pneumatic impact canon. At this, the granules are pneumatically accelerated and impact on a rigid impact plate. The specific breakage energy distribution and also the breakage velocity distribution have been determined. The obtained results have been used for evaluation of the results gained by the presented quasi static compression tests. A good agreement has been achieved.

16. A COMBINED EXPERIMENTAL AND MODELLING INVESTIGATION OF THE IMPACT OF POWDER PROPERTIES

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In this work we present a combined experimental and modelling approach to understanding the wet granulation of lactose powder in a high-shear mixer. Experimental data is produced by performing nine granulation runs using lactose monohydrate as the initial powder and deionised water as the binder. The granulation runs were performed with variations in impeller speed, massing time and binder addition rate. The granulation process is then simulated by a population balance model containing five rate parameters requiring estimation. A sensitivity study of the model reveals two important properties which have been the subject of further experimental work. First, the model input value that quantifies the height of the asperities on the particles is found to limit the model's ability to produce large particles. However, by allowing the parameter for the height of asperities to vary over a range while estimating the rates, the simulated particle size distribution agrees well with the experimental one when using a single value characterisation. Second, the input parameters which describe the initial particle size distribution are found to significantly affect the distribution of the end product. When the input parameters which define the dispersion of the initial powder are allowed to vary, the model demonstrates an ability to simulate the experimental empirical size distributions. Both of these characteristics of the initial powder have been investigated further.

18. INTERACTIONS BETWEEN BACTERIA AND MILK PROTEINS: INFLUENCE ON ENCAPSULATION EFFICIENCY

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Interactions between bacteria and milk proteins are believed to influence the encapsulation efficiency and the location of the bacteria in the microparticle. The objective of this work was to quantify interactions between *Lactobacillus rhamnosus* GG and milk proteins (micellar casein, native and denatured whey proteins).

AFM force measurements were realised by immobilising the probiotic bacteria on the AFM tip (lacto probe). Milk proteins were deposited on mica surfaces by forming a thin layer. The functionalised tip was used as a force probe to measure the interaction forces between the bacteria and milk proteins on the nanoscale. AFM force measurements described non-specific adhesion between bacteria and micellar casein and specific adhesive events between bacteria and whey proteins (Figure 1).

Concurrently, microencapsulation of the bacteria was realised in different milk protein matrices. The best encapsulation rate was obtained by addition of denatured whey proteins whereas the lowest one was obtained for a matrix containing only micellar casein (Figure 1). The bacterial survival along the gastric digestion was also improved by an encapsulation in a matrix containing denatured whey proteins. It can be concluded that specific interactions between bacteria and milk proteins has a positive influence on encapsulation, particularly on the encapsulation rate and survival during simulated gastric digestion.

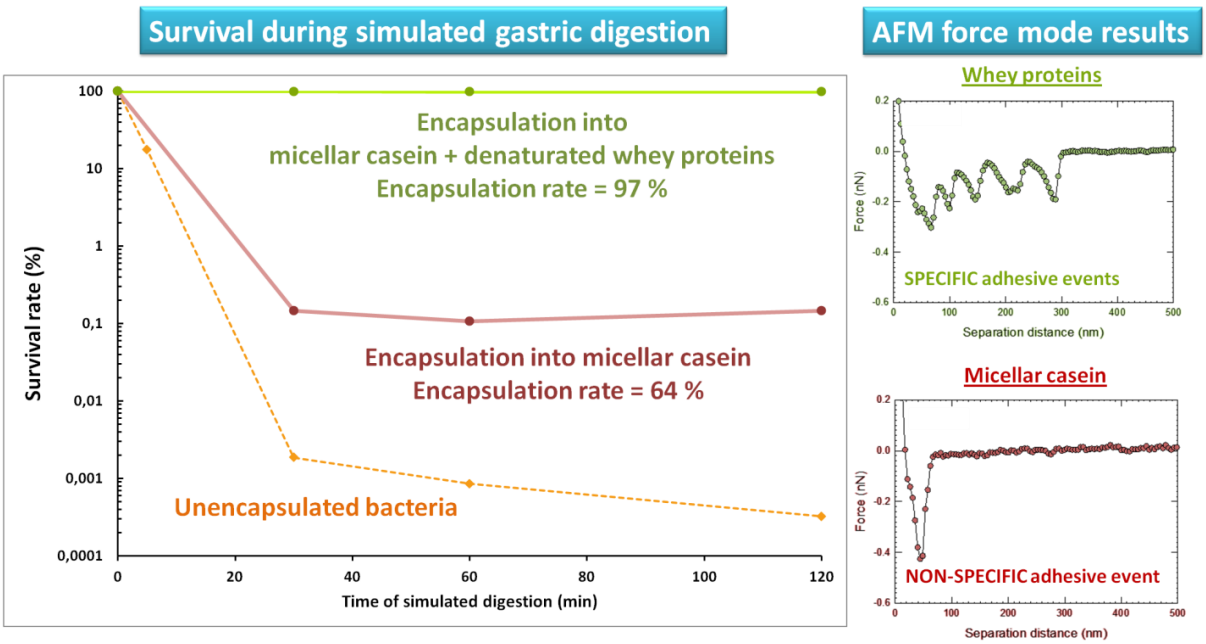

Figure 1 : Interactions between milk proteins and bacteria linked to the encapsulation efficiency

20. EFFECT OF PROCESSING ON THE STABILITY OF ANHYDROUS OLANZAPINE

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2 Pharmazeutisches Institut, Eberhard Karls Universität Tübingen, Auf der Morgenstelle 8, D-72076 Tübingen, Germany

APIs are frequently exposed to water in several pharmaceutical processes (e.g.crystallization, wet granulation) which may induce the production of hydrates [1]. Also, during certain manufacturing steps (drying, tabletting) the hydrates formed in the process could dehydrate and a metastable anhydrous or an amorphous form could be obtained [2]. These modifications are likely to affect the bioavailability of the drug, requiring a particular control over these processes. The present study was focused on the ability of olanzapine to suffer pseudopolymorphic transitions during the manufacture of pellets by extrusion-spheronization.

Extrudates, with the same fractions of olanzapine (15%w/w), excipients, (MCC, 75%w/w; PEG-6000, 10%w/w) and water (75%, based on the dry powder mass) were manufactured. 50% of the formed mass (#1.1) was extruded immediately whereas the remaining (#1.2) was left to rest in a hermetic container for 24 hours, prior to extrusion. Pellets were manufactured from the extrudates in a spheroniser (500rpm) for 5 minutes. Wet pellets were dried in a fluid bed drier at 45°C for 30 min (Aeromatic). XRPD and FTIR analysis were considered to detect and characterize different solid phases of olanzapine in all pellets' manufacturing steps.

The pellets #1.1 and #1.2 presented significant differences on loss on drying, strength, density and porosity proprieties, which are not detected in placebo pellets. One explanation to all these modifications are related to the hydration of olanzapine into 2 hydrated forms during the resting time of the wet mass, which is verified by XRPD and FTIR. The drying of the pellets #1.2 for 30/60/120 minutes at 45^{o}C was not enough to remove one of the hydrated forms of olanzapine. This result shows the relevance of understand mechanism of dehydration of hydrated forms of olanzapine. Although the resting time of the mass contributes to a narrow size distribution of the pellets due to a better distribution of water, the pseudopolymorphic transformations of olanzapine during the resting time, together with physical alterations on the final product (pellets) promoted by its solid-state changes, influence negatively the dissolution rate of the olanzapine pellets.

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21. THE USE OF ATOMIC FORCE MICROSCOPY (AFM) IN INVESTIGATING PARTICLE CAKING MECHANISMS

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Unwanted agglomeration, or caking, is a persistent problem in the powder processing sector. With the development of complex multi-component formulations which often contain sub-micron particles, conventional anti-caking measures may be insufficient and new methods to maintain quality are required. This work aims to supplement bulk testing by examining surface changes on particles and interparticle bridge formation using Atomic Force Microscopy (AFM). As a non-destructive method, AFM can be used to repeatedly scan areas exposed to humidity cycling [1-3]. This has produced scans showing changes in particle surface topography, composition and stickiness. Amorphous particles show surface viscous flow when exposed to high humidity, with multi-component particles showing a redistribution of components. AFM has also been used to profile the formation of interparticle bridges between spray-dried particles, contrasting real systems with the simplified model proposed by Rumpf [3-4].

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[3] D.C. Prime, M.C. Leaper, J.R. Jones, D.J. Richardson, C.D. Rielly, A.G.F. Stapley, Caking behaviour of spray-dried milk powders - using scanning probe microscopy to study nanoscale surface properties, Chemical Engineering and Technology, 34 (7), (2011) 1104-1108.

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22. STABILITY AND REPEATABILITY OF A CONTINUOUS TWIN SCREW GRANULATION AND DRYING SYSTEM

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Using a continuous granulation technique, the amount of material processed is only determined by the time the process is operating under specific process settings. Whereas this provides tremendous flexibility and eliminates technology transfer, it is essential that the process continuously operates under steady state conditions to manufacture granules of a specific quality for any length of time. The aim of this study was to determine the robustness of the wet granulation process using the ConsiGma™-25 system (a continuous tablet manufacturing system) during long production runs by monitoring process parameters, granule properties and tablet quality in function of time. In order to investigate the repeatability, a 5h run was performed in triplicate.

A premix of two active ingredients, powdered cellulose, maize starch, pregelatinized starch and sodium starch glycolate was granulated with demineralized water. Experiments were done using the ConsiGma™-25 system which consists of a high shear wet granulation module (based on twin screw granulation), a six-segmented fluid bed dryer module and a granule conditioning unit. After drying and milling (1000µm, 800rpm), granules were directly compressed using a Modul™ P tablet press (tablet weight: 430 mg, main compression force: 12 kN). Granule (PSD, LOD, flowability) and tablet (weight uniformity, hardness, friability, disintegration time and dissolution) quality was evaluated in function of time.

PSD of milled granules consisted of 20.2 ± 0.5 % fines (<75µm) and 27.9 ± 0.3 % coarse granules (>500µm). LOD after drying was 1.38 ± 0.02 %. As the Hausner ratio was 1.22 ± 0.01, the granules are classified as fairly flowing. Tableting resulted in acceptable hardness (89.0 ± 8.0 N) and weight uniformity. Friability of tablets (0.15 ± 0.01 %) allowed subsequent coating. For all tablets, the disintegration time was low (<4 min) leading to complete release of both APIs after 30 minutes. Generally, no trend in granule and tablet properties was observed in function of time. Besides, no deviant granule and tablet quality was observed during start up and shut down phase.

For multiple hours, granule and tablet quality was constant in function of time and complied with the product specifications. Consequently, the ConsiGma™-25 system can be considered as a robust and reproducible system for the continuous production of tablets via wet granulation.

26. SPRAY ZONE DEMARCATION IN TOP-SPRAY FLUIDISED BED GRANULATION BY DROPLET DETECTION METHODS

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The granulation of particles is frequently realised in fluidised beds. The often applied technology of top-spray granulation shows advantages in process simplicity and in the ability of producing agglomerates of powders. In the process, the atomisation of binder liquid has significant impact on product quality, process stability and process performance. In order to visualize the influence on the process dynamics, different methods of experimental acquisition and numerical simulations on a coupled DEM-CFD approach are exerted. In the experimental investigations the spray expansion, the spray penetration into bed and the particle wetting are observed. The results yields a process separation into two characteristic compartments. The compartment sizes are determined in dependence on the spray characteristic. The spray compartment is defined by the occurrence of active binder droplets available for the build-up of particle structures. For the estimation of compartment size the electric conductivity of water as binder agent has been used to derive the droplet appearance in the system. For the size-estimated compartments, particle masses, particle velocities, residence times and re-circulation behaviour have been obtained by image based measurements such as Particle Image Velocimetry and Digital Image Analysis.

A more detailed observation of spray and droplets occurrence can be done by numerical DEM-CFD simulation. In the coupled simulation approach of top-spray granulation, the fluidisation gas flow has been considered as a continuum applying a mesh based finite volume solver. The particles and the droplets have been considered as discrete elements. Here, dynamics of droplets and particles, their interactions and collisions can be studied on single element scale in bubbling fluidisation condition. Detailed information, for instance the spatial wetting of particles, droplet distribution, droplet residence time or the mass estimation of droplet overspray, can be concluded from the simulations.

The performed investigations show that there is a strong dependence of the results on the nozzle position in the bed. Along with position, the amount of fluidisation and the nozzle pressure show significant influence on the spray compartment size and the particle residence times. Finally, acquired parameters are inserted into a compartment population balance model (PBM). Results are compared with data obtained from experimental trials, and the achieved model enhancements are illustrated.

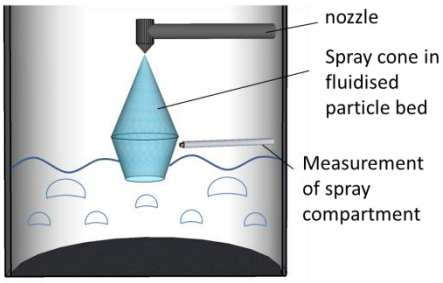

Fig 1: Probe measurement in fluidised bed for spray compartment identification

27. STOCHASTIC MODELLING OF FLUIDISED BED SPRAY AGGLOMERATION TRACKING PARTICLE STRUCTURE

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The mathematical description of fluidised bed spray agglomeration is here formulated by an alternative Monte Carlo approach [1], which is a fully predictive, stochastic solution attempt. Rather than fitting kinetic expressions from experimental data, it can be used directly to compare with simulation results. Furthermore it can handle a large number of particle properties, while the classical deterministic population balance is usually expressed with one (particle size) or two internal coordinates (water mass on particles). The Monte Carlo model evolves a discrete sample of 1000 particles representing the distributed properties (particle size, porosity, moisture) of the real process in time. A scaling factor correlates the simulation box and the real system [2]. It determines the simulation step which is equivalent to the length of time between two binary particle collisions. Second, it correlates the number of sample particles with the frequency of droplets entering the model system per unit time. Free droplets undergo drying after being inserted and either dry out or get deposited on the particles. The change of initial particle properties is caused by physical processes taking into account thermodynamic (drying and penetration of droplets) and mechanical influences (collision of particles, breakage). They have been modelled and validated by experiments separately.

Results are shown for a batch granulator, operated in top-spray configuration. Experimental results won in that granulator will be compared to the simulation output. The presented results will contain the general outline of the Monte Carlo method, such as selection of sample size and its regulation throughout the process. The scheme of incorporated micro processes and their interaction on a macro scale will be discussed. The second key aspect of the presentation will be the evaluation of the full 3D particle structure. Every particle features its own history of aggregation, breakage and consolidation during the process. Morphological descriptors, such as particle porosity or coordination number, will be evaluated for the simulated agglomerates and are compared directly to particle characterization done via computer X-ray tomography [3].

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28. ROLL COMPACTION OF GRANULATED MANNITOL GRADES AND THE UNPROCESSED CRYSTALLINE DELTA-POLYMORPH

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Dry granulation by roll compaction is a widely used technology in pharmaceutical industry. Most commonly used fillers are microcrystalline cellulose and lactose monohydrate, whereas the application of mannitol in dry granulation processes is not well documented. However, mannitol is an excipient of growing importance due to its low drug interaction potential, its high solubility (required for orodispersible formulations) or its good physiological compatibility.

In this work untreated, crystalline mannitol was roll compacted at various specific compaction forces (2, 6 and 10 kN/cm). The resulting granules were characterized with regard to their particle size distribution, flow property and BET surface area. It was found that an increased compaction force led to granules with improved flowability due to a lower amount of fines (particles ≤ 90 µm). Furthermore, BET surface area of the granules increased after dry granulation with higher compaction forces. This can be explained by the distinct fragmentation behaviour of brittle mannitol [1]. Although the surface area of granules increased when applying higher compaction forces, tensile strength of drug-free, 10 mm flat faced tablets decreased due to the work-hardening phenomenon [2]. In comparison to tablets made of roll compacted granules of spray-dried mannitol with considerable larger surface areas tablets made of untreated, crystalline mannitol exhibit inferior tensile strength [3].

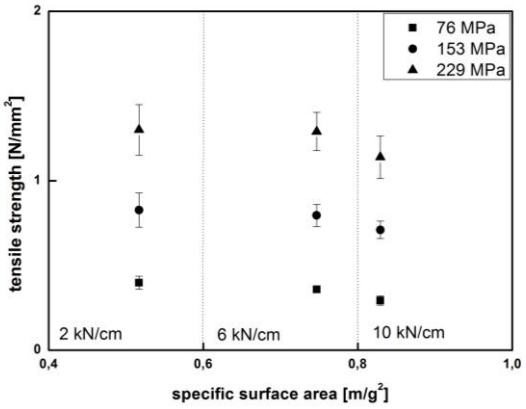

Figure 1: Tensile strength of tablets compressed with various compression forces plotted against the specific surface area of the investigated granules.

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30. A VALIDATED FLOWSHEETING TOOL FOR THE STUDY OF INDUSTRIAL GRANULATION PROCESSES

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Nowadays, process simulators that accurately model real plant operation are commonly used for design, simulation, troubleshooting and optimization purposes [1,2]. Process modelling plays a key role in improving industry productivity, especially for large-scale plants with high energy consumption. Small process improvements often lead to great benefits in terms of overall plant performance [3]. However, most of the progress achieved in flowsheeting tools has been focused on fluid processes (i.e., the most traditional liquid/gas based industries). Indeed, the modelling of processes involving powders or granules is difficult because, among other reasons, they are distributed systems that have to be described by complicated mathematical functions. Consequently, the representation of solid processes is not a trivial task due to the complexity of the partial integro-differential equations associated to changes in particle properties distributions [1-3].

Within solids processes, granulation is one of the most important operations. In the fertilizers industry, it particularly provides products with high resistance to breakage and low tendency to caking and lump formation [4]. The operation of granulation circuits, which include not only particle size enlargement in the central granulator but also particle size classification in screens and particle size reduction in mills or crushers, is generally not simple and due to operational challenges the capacities are much less than the nominal ones with high recycle ratios that overload all process units [5,6]. Moreover, industrial circuits are usually operated by trial and error, being difficult to run the plants at steady state without frequent undesired shut-downs.

In view of the above-mentioned difficulties, this work evaluates the capabilities of a complete dynamic simulator developed for a urea granulation circuit (based on fluidized-bed granulation) to analyze the process sensitivity against different disturbances and to study common operating problems. First, the circuit model is validated by comparing simulation results with experimental data from a high capacity plant. Based on a sensitivity analysis of the process variables, diverse strategies are explored aiming to solve typical operational challenges (i.e., too high granulation temperatures, undesired dust formation, units overload, plant capacity increase, product quality control, etc.) by considering different control loops or alternative flowsheets configurations.

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31. MEASUREMENT OF FLOW PROPERTIES OF PULVERIZED COAL WITH DIRECT SHEAR TEST

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In this work, flow and physical properties were measured for two typical Chinese coals (Beisu and Yangchangwan pulverized coals) used in the process of the entrained-flow pulverized coal gasification. Besides powder physical properties, e.g., particle size, moisture content, bulk and particle densities, powder flow properties were investigated using the direct shear test of ShearTrac-II system. The pulverized coals show small particle size and strong interparticle interactions, easy to form agglomerates, typical of cohesive powders. The flow properties of pulverized coal, as characterized by the angle of repose, the linearized inner friction angle and the effective angel of internal friction, the powder cohesion, the unconfined yield strength, flow index and the wall friction angle were determined, and then compared and discussed. The pulverized coals show strong friction effects and poor flowability, far different from cocoa and cheese, but somewhat approaching to cement and taconite. On the other hand, wall friction angle was measured which is considered to be depended on both powder properties and wall materials. The irregular particle shape of pulverized coal and the large friction effects of carbon steel result in the large wall friction angles between coal samples and carbon steel wall.

ShearTrac-II system

32. IMPACT OF CONCENTRATED COLLOIDAL SUSPENSION DROPS ON SOLID SURFACES

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When droplets of high concentration wet powder impact on a solid surface, the large stresses that build up upon impact may convert them to a stable system of dry granules. Dilation/jamming has been proposed to explain such powder granulation processes [1]. Stress causes dilation of particles into the droplet surface, against capillary pressure, roughening the surface on the scale of the constituent particles. Under the right conditions of stress magnitude and particles concentration, the droplet jams internally in response to capillary pressure, forming a mechanically stable granule. This remains a tentative model of granulation, which despite its importance in process industries ranging from minerals to foods to detergents, remains unexplained.

This work presents the preliminary results of drop impact experiments of a suspension of near hard-core colloidal particles, with the purpose to investigate the impact morphology in the presence of shear thickening or jamming, which may be induced by the large velocity gradients arising upon drop impact. In particular, drops of a suspension of nearly hard-core particles in octadecene (volume fraction: 59.6%) impacting on substrates of different wettability is studied experimentally by high-speed imaging, for impact Weber numbers ranging between 26 and 262. Upon impact, these drops do not exhibit inertial spreading, which is observed for other Newtonian and non-Newtonian fluid drops. On wettable surfaces (glass), impact is followed by capillary-driven spreading at the same rate observed in Newtonian fluids (Tanner's law), while on less wettable surfaces (PTFE) colloidal suspension drops relax to achieve the shape of a spherical cap, but do not spread. This peculiar impact morphology, and in particular the absence of inertial spreading, is interpreted as a consequence of dilatancy and jamming occurring upon impact.

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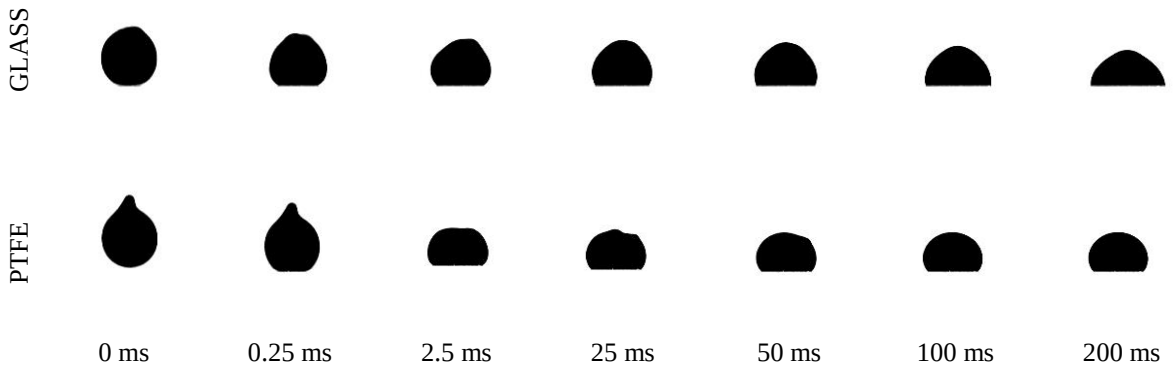

Drop impact morphology of colloidal suspension drops (volume fraction: 59.6%) impacting on glass and PTFE surfaces.

33. ALGORITHM PARALLELIZATION OF COUPLED CFD-DPM FOR LARGE SCALE DENSE PARTICULATE FLOWS

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Development of parallel CFD-DPM algorithms under shared-memory multiprocessor environments has surfaced some difficulties. This is particularly true for dense systems since within one time step one particle can be enduring contacts with many particles populating different processors. Mutually exclusive access to the particle contact force data among all processors is necessary to keep the data consistency but this will lead to a dramatically depressed parallel efficiency. These severe shortcomings limit the range of applications of this type of parallel DPM algorithm and make it suitable only for granular flows simulations where inter-phase coupling is of trivial significance and the fluid flow is of no interest. Since most of the CFD codes are parallelized under distributed-memory parallel computing environments, some attempts have been made to develop parallel DPM algorithms for dense particulate flows under the same parallel architecture. For such a development, it is very difficult to achieve efficient load balancing of processors due to the heterogeneous particle spatial distribution that often characterizes dense particulate systems.

In a previous work [1], the authors have developed a serial robust hard-sphere discrete particle model on 3D unstructured mesh. A multifaceted numerical strategy was designed to solve the numerical difficulties related to the use of generic 3D unstructured meshes and to enhance the DPM's numerical efficiency. In this work, the serial DPM algorithm was redesigned to accommodate the time-driven soft-sphere approach. Algorithms shared by both hard- and soft-sphere models were re-used and extended to distributed-memory HPC environment. Parallelization-generated numerical difficulties such as void fraction calculation, two-phase momentum exchange, and efficient contact force calculations for particles at irregular and arbitrary partition boundaries were efficiently addressed. The load-balancing difficulty due to heterogeneous particle distribution was overcome by the introduction of multi-threading. An efficient algorithm is proposed to handle data-exclusive access of the shared-memory by multi-threads in a compute node. To the best knowledge of the authors, there are no literature reports on the parallel CFD-DPM algorithm development under distributed memory environment with a fluid flow solver based on finite volume method and arbitrary 3D unstructured meshes

The developed parallel DPM model has been successfully used to simulate many important applications such as particle mixing in bubbling fluidized beds, granular Rayleigh-Taylor instability during sedimentation, and cylindrical spouted beds to name only few.

[1] C.L. Wu, A.S. Berrouk, K. Nandakumar, Three-dimensional discrete particle model for gas-solid fluidized beds on unstructured mesh, Chemical Engineering Journal, 152 (2009) 514-529.

34. COMPRESSION PREDICTION ACCURACY FROM SMALL SCALE COMPACTION STUDIES TO PRODUCTION PRESSES

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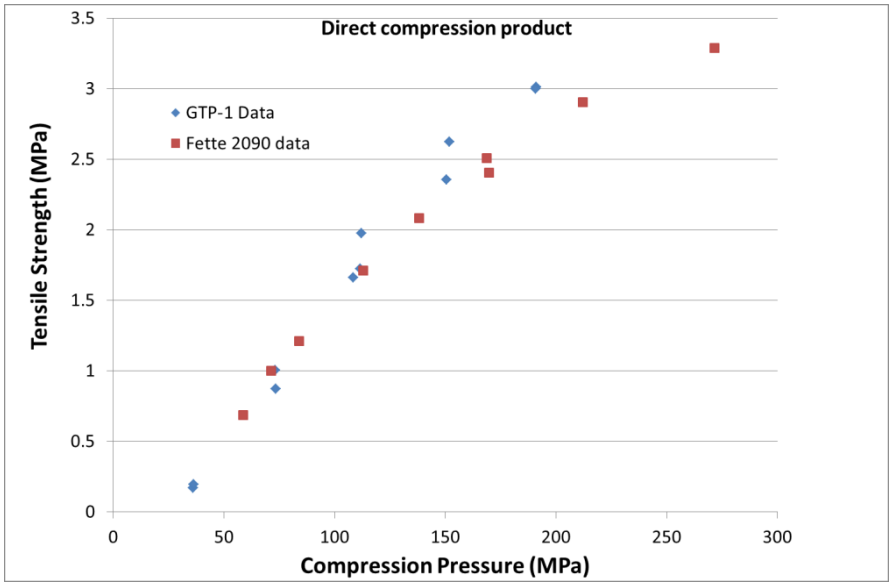
A major issue in using small scale compaction studies to address manufacturing and development challenges is the validity of extrapolating the data and predictions across the scales. In this paper a systematic approach is presented to characterise tablet manufacturing by compressing milligram quantities of material from a bench top press (Gamlen Tablet Press GTP-1) and using this data to predict accurately the tablet quality for large scale rotary tablet presses (Fette 2090) used in the manufacture of commercial products.

The compressibility of two formulations of commercial products were compared on the GTP-1 and the Fette 2090. One formulation was produced by direct compression (DC) and the other by wet granulation (WG). 100mg of each formulation were compressed using the GTP-1 at various compaction forces between 1 to 5kN to form 6mm round-faced tablets. Data was collected on the compression profile, ejection stress, weight, thickness and fracture strength of the tablets formed. Data was similarly generated from production runs of the formulations on a Fette 2090 tablet press. In this case 800mg (for the DC) and 1140mg (for the WG) caplet-shaped tablets were produced at forces ranging from 6 to 30kN providing a great contrast to the small scale round 100mg tablets.

Comparison was facilitated by transforming the data to compaction pressure, tensile strength, solid fraction and shear strength for the two formulations and presses. Analysis of tablet properties in this way clearly demonstrated that the results obtained on the GTP-1 could be predictive for the tablets produced on the Fette 2090. So providing an excellent method to predict commercial manufacturing with only minimal quantities of materials.



Comparison of data generated from small scale compaction study (GTP1 press: 100mg round tablet) to full scale manufacturing press (Fette 2090 press: 800mg caplet shape)

35. MELT GRANULATION: EFFECTS OF OPERATING VARIABLES ON PARTICLES GROWTH MECHANISMS

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Granulation processes are usually classified according to the binder nature as wet, dry o melt. Nowadays, dry or melt granulation are considered attractive strategies to overcome operating problems caused by moisture.

The amount of articles related with wet granulation processes using aqueous solutions as liquid binders is vast. Among others, Smith and Nienow [1], Pont et al. [2] and Hemati et al. [3], studied the influence of the process variables on the particles growth kinetics when aqueous solutions are atomized into beds of solids fluidized by hot air. These experimental studies revealed that many variables can affect the particles growth mechanisms: binder (composition, viscosity, surface tension, flowrate, droplet size), seeds properties (size, shape, porosity), atomization and fluidization air flowrates, nozzle location, bed temperature, etc. For wet granulation and low excess gas velocities, agglomeration was identified as the main particle growth mechanism. For higher gas velocities, the higher particles circulation rate improved the liquid distribution on the seeds surface, reducing bed quenching by lumps formation. Moreover, the higher gas velocities increased the frequency and energy of the inter-particle collisions and particle-wall impacts that are responsible for the breakage of the solidified binder bridges formed between primary seeds. The same behaviour was observed, through experimental work, for different fluidized granulation systems (i.e., with different operating variables and material parameters). Besides, the growth regions were found to be very sensitive to the product and type of granulation unit.

Unfortunately, the theories and results obtained for wet granulation are not fully appropriate for describing fluidized-bed melt granulation [4,5]. As for wet granulation, many authors were focused on identifying the influence of some of the more important experimental variables on the product quality. Regarding the studies based on fluidized-bed granulation by atomizing molten binders, Abberger et al. [6], Seo et al. [7], Tan el al. [5] and Boerefijn and Hounslow [8] investigated the effects of binder spray rate and droplet size, seeds size, bed temperature, atomization air pressure and fluidization air velocity on the process performance, using polyethylene glycol as a model binder and glass ballotini or lactose as seeds. In addition, the binder flowrate and the seeds sizes were relatively low. In this work, the influence of the operating variables of a pilot-scale fluidized-bed granulator (binder flowrate, fluidization air velocity, bed temperature, atomization air flowrate and seeds sizes) on the urea particles growth mechanisms is studied. Particularly, relatively large urea seeds (from 1.5 to 3.7 mm) and high binder flowrates (between 0.24 and 1 kg/min of molten urea; for a bed mass of about 2 kg) were used. The results indicate that the melt flowrate and the fluidization air velocity strongly affect agglomerates formation. A regime map, derived from the performed experiments, is presented to predict the process variables ranges that guarantee the production of granules by coating.

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40. TRANSFER OF BATCH FLUID BED GRANULATION TO A CONTINUOUS PROCESS – CASE STUDY

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The majority of tablets are compressed from granulates due to improved properties in comparison to powder mixtures. Fluid bed granulation plays an important role for granulate manufacturing. A severe demand arises for a process transfer from batch to continuous mode for large volume drug products. This transfer was successful performed with a placebo formulation and a market product [1, 2] but one should take into consideration that in each single case the process parameters as well as the properties of the formulations exhibit strong influence on the feasibility of the continuous process. In this study, the process transfer of a market product was investigated what is characterized by several problems: sparingly soluble drug substance, high granulation liquid demand for successful agglomeration and a specified relatively low granulate size.

On the base of the actual batch production process parameters the fluid bed granulation process was performed and validated in batch laboratory scale (fluid bed granulator GPCG 1.1, Glatt GmbH). For the continuous process a fluid bed granulator GF 25 (ProCell system, Glatt GmbH) was used. Granulates were compressed into tablets, and granulates as well as tablets were tested according to the product specification and pharmacopoeia.

The batch fluid bed granulation process was stable, gave high yields and led to specified products with high spray rate, high process air temperature and additional granulation with water for sufficient agglomeration. Three validation lots were manufactured. The product parameters (granulate and tablets) fulfilled the acceptance range. The continuous fluid bed granulation process was strong sensitive to the interaction of process air temperature, powder feeding rate, granulation liquid spray rate and product discharge rate. With the submission of a sufficient amount of start granulate the continuous process reached steady state after two hours and the process was investigated in steady state over three hours. Samples were withdrawn for granulate testing and tablet compression. Properties of granulates of the continuous process scattered in a narrow range and were similar to the batch products. Also the tablets referred to the specified demands. On the base of a validated fluid bed granulation process in batch laboratory scale the continuous pilot/production process was successful established offering the advantages of reduced process time and energy consumption, low contamination risk and reproducible product quality over a long production time period.

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[2] Germer, K., Zenker, M., Jacob, M., Wolf, B.: Transfer of a batch fluidized bed granulation to a continuous process. ACHEMA 2012, Frankfurt, Germany, 2012-06-18/22

42. MODEL-BASED CONTROL OF PARTICLE PROPERTIES IN FLUIDISED BED SPRAY GRANULATION

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Granulation is an important process in many industries, for example foods, detergents, pharmaceuticals, and fertilisers. The aim often is the production of a solid, free-flowing powder from solutions or suspensions, because powders are often easier to handle, to transport or to store than their liquid basis components. Additionally, it is possible to change properties of the particles in the powders where the final product quality can often be characterised by the particle properties, for example the size, volume, moisture content, or enthalpy (temperature). In general each particle has its own values for the characteristic properties, i.e. the particles are not uniform but possess a property distribution.

One process that is widely applied for particle formulation is fluidised bed spray granulation: Due to fluidisation of the particles by hot gas, the sprayed liquid evaporates and the solid content forms a layer on the surface of the particles in the bed. This multi-phase process involves heat and mass transfer (liquid to solid) and particulate processes (growth of the layer).

Spray granulation processes can be run in a continuous way. There, particles are removed from the bed and after classification the portion that does not comply to the required specifications is re-fed into the apparatus for further treatment. The classification can be performed internally by a classifying outlet or externally by screening and milling. In both cases the property distribution of the particles in the bed determines the product mass flow and product characteristics. Also, depending on the parameterisation of the processes, they are either open-loop stable or unstable, exhibiting a nonlinear oscillation in the particle size distribution and the product mass flow. It is thus of high importance to monitor and control the property distribution in the bed in order to guarantee a product that complies to still increasing product requirements.

In this contribution different control approaches, ranging from standard linear control to non-linear model predictive control, are applied to fluidised bed spray granulation processes with internal and external product classification. These processes exhibits sustained non-linear oscillations in the particle property distribution, i.e. size distributions that have negative influence on steady-state operation, e.g. constant product mass flow with constant properties. The controllers are applied to stabilise these open-loop unstable steady-states. Additionally, the heat and mass transfer during particle formation is influenced in such a way that a desired product moisture and temperature is obtained.

43. EXCIPIENT PROCESS INDUCED TRANSFORMATIONS (PIT) PRODUCED BY HIGH SHEAR WET GRANULATION

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The physical form of an active drug substance is usually carefully selected for final dosage form manufacture; however the subsequent processing conditions will also determine the solid state of the drug in the final product. While phase transition of API during pharmaceutical processing has been the subject of numerous investigations, such transformations in excipients, either during product manufacture or storage, have not been adequately addressed. This lack of understanding is of concern because the properties of a solid dosage form can also be influenced by the excipients[1] .

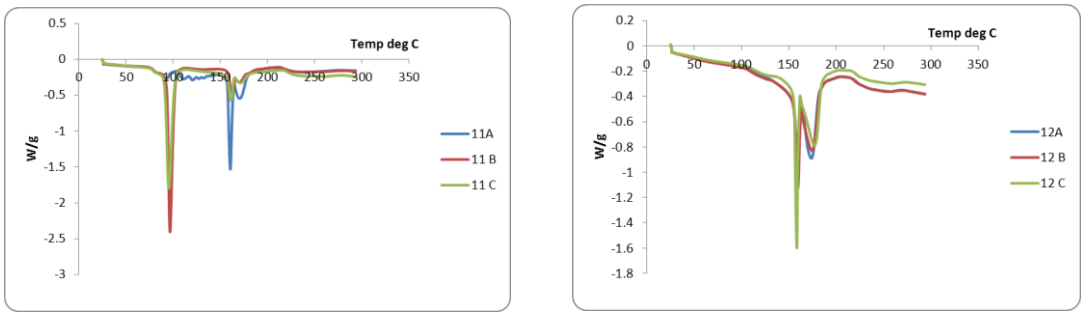
Research has indicated that the properties of calcium hydrogen phosphate dihydrate (CHPD) such as crystal structure, particle size and shape, particle aggregation structure and susceptibility to dehydration at low temperature in the presence of water vapour, can vary depending on conditions prevailing during manufacture and even the country of origin [2, 3]

In this work granules produced by a variety of granulation settings showed two distinct the differential scanning calorimeter (DSC) profiles indicating changes had occurred. Some of the runs had a strong endotherm at 100°C which has been linked to the hydrate state of the excipient CHPD. The research further investigates the influence of process induced transformations (PIT) on final product dissolution and seeks to map the stressed processing regime using high shear wet granulation.

[1] T. Miyazaki, K. Sivaprakasam, J. Tantry, R. Suryanarayanan, Physical characterization of dibasic calcium phosphate dihydrate and anhydrate, Journal of Pharmaceutical Sciences, 98 (2009) 905-916.

[2] M. Landín, R. Martínez-Pacheco, J.L. Gómez-Amoza, C. Souto, A. Concheiro, R.C. Rowe, The effect of country of origin on the properties of dicalcium phosphate dihydrate powder, International Journal of Pharmaceutics, 103 (1993) 9-18.

[3] M. Landín, R.C. Rowe, P. York, Particle size effects on the dehydration of dicalcium phosphate dihydrate powders, International Journal of Pharmaceutics, 104 (1993) 271-275.



DSC profiles from granules of identical composition but processed using different granulator settings showing distinctly different DSC curves

45. FLOW PATTERN AND STABILITY ANALYSIS IN PNEUMATIC CONVEYING OF PULVERIZED COAL IN AN INDUSTRIAL-SCALE HORIZONTAL PIPE

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Dense phase pneumatic conveying of pulverized coal was conducted in an industrial-scale horizontal pipe (50mm I.D.) using air as carrier gas. Minimum pressure drop velocity from the Zenz-type phase diagram, flow pattern as well as its conveying stability was investigated. Based on both the electrical capacitance tomography system and the visual methods, the flow was classified into three patterns: stratified flow, moving bed flow and slug flow. Using the methods of probability density function and power spectral density function, the pipe pressure time series were also analyzed, and found that they were well correlated with flow patterns. As a result, the critical velocity between stable and unstable conveying was achieved.

46. AGGLOMERATION TENDENCY IN DRY PHARMACEUTICAL GRANULAR SYSTEMS DURING BLENDING: DE-AGGLOMERATION MODELING APPROACHES

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Efficient blending of powders is of critical importance in the manufacture of a wide variety of industrial products, including pharmaceuticals, foods, plastics and agrochemicals [1, 2]. This study determined the influence of geometry of blenders (double cone blender and V-blender), blending speed and time. The blend composed of diclofenac sodium, microcrystalline Cellulose, starch, magnesium stearate and talc. It was subjected to homogeneity assessment, size analysis, drug-excipient analysis and dissolution studies.

Fourier transform infrared spectroscopy (FTIR) analysis of the blend showed that there was no chemical interaction. Then, the blend was added seperately to the two blenders and tested at 25, 50 and 75 rpm at 5, 10 15 and 20 mins. For testing the homogeneity (uniform distribution of diclofenac sodium), content of diclofenac sodium was determined and was found that it ranged from 65.2-74.3% at low speed to 85.4-96.7% at high speed. The dissolution profiles showed an unusual flat asymptote indicating incomplete extents of dissolution (54-65%) with blending at low energy rates and short mixing times (5-10 min at 25 rpm) possibly caused by agglomerates that did not readily disperse in the dissolution medium. The study showed that increasing both speed and time of mixing (15-20 min at 75 rpm) enhanced the extent of dissolution (91-96%). Mixing speed and time had much greater influence on the extent of dissolution which was controlled by deagglomeration than on the initial dissolution rate, which in turn was related to the dispersed diclofenac sodium. The V-blender appeared to operate intermittently, combining splitting and merging, while the double-cone appeared to operate continuously, with a nearly constant flow of particles in a more uniform surface layer. This resulted in significantly more rapid mixing in the V-blender than in the double cone. Nevertheless, both exhibited reproducible and rapidly occurring segregation patterns.

The blending conditions influenced the mixing quality of agglomerate characteristics. The use of particle sizing approaches to construct deagglomeration profiles and their interpretation using modeling approaches provided parameters representing agglomeration and deagglomeration rate constants.

[1] L.T. Fan, Y.M. Chen, F.S. Lai, A Theoretical Study of Deposition of Charged Particles in a Convergent Channel Due to Image Forces, Powder Technology, 61 (1990) 225-229.

[2] M. Poux, P. Fayolle, J. Bertrand, D. Bridoux, Powder mixing: Some Practical Rules Applied to Agitated Systems, Powder Technology, 68 (1991) 213-234.

47. EFFECT OF LIQUID LAYERS ON ENERGY DISSIPATION DURING OBLIQUE IMPACT OF DRY SPHERES

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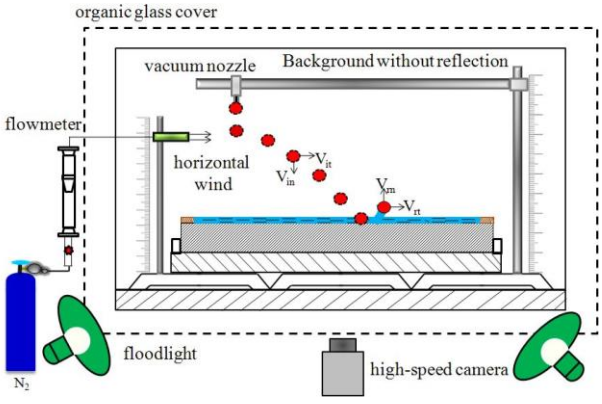
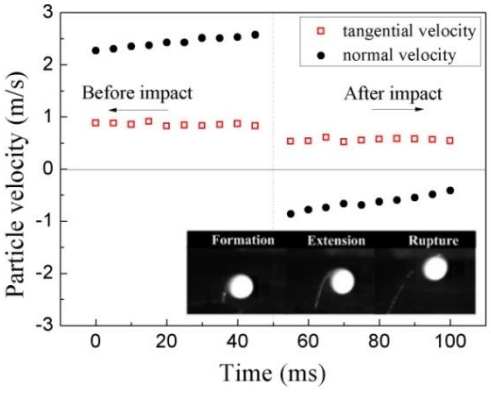
In fluidization granulation process, particles are coated with a liquid layer. This causes the particles to exhibit different impact and rebound behaviours compared with dry particles, when interacting with each other due to the formation of liquid bridge. Therefore, an understanding of the impact behaviour of particles on a liquid layer should assist in the design and control of granulation process. In recent years, the normal impact of particles on the liquid layer has been extensively investigated. However, the oblique impact and rebound behaviour of particles, as well as the energy dissipation associated with the impact are still lacking.

The purpose of this paper is to explore the effect of liquid layer and impact velocity on the energy dissipation through an experiment by tracing oblique falling spherical particles impacting on a wet surface. Free-fall Al_2O_3 particles disturbed by a horizontal gas flow would exhibit normal and tangential velocity simultaneously. The aqueous solutions of hydroxypropyl methylcellulose were employed as liquid layer with different concentrations for variation of viscosity. The movement of particles was recorded by a high-speed video camera and subsequently analysed to determine particle velocity, based on which, the normal and tangential restitution coefficients of particles were obtained.

It was found that the oblique impact exhibits significantly different impact and rebound behaviour in comparison to the normal impact. Due to the rolling on the wet surface, the oblique impact particles rebound with certain angular velocities, which forms a similar cylindrical shape of liquid bridge rather than the pendular bridge formed during the normal impact. The values of particle velocity corresponding to the shape of liquid bridge were obtained to realize the effects of liquid bridge force. In the current work, the coefficients of normal and tangential restitution of oblique impact particles were also studied as a function of the tangential velocity and various liquid properties. Based on the experimental data, a model taking into account various forces acting on the particles was proposed to derive the kinetic energy dissipation process. The predicted restitution coefficients were compared with the experimental data to validate the accuracy of the model.



Schematic of the experimental apparatus



Snapshots after impact and corresponding velocity versus time

48. INFLUENCE OF PROCESS VARIABLES ON PARTICLE MORPHOLOGY IN SPRAY FLUIDIZED BED AGGLOMERATION

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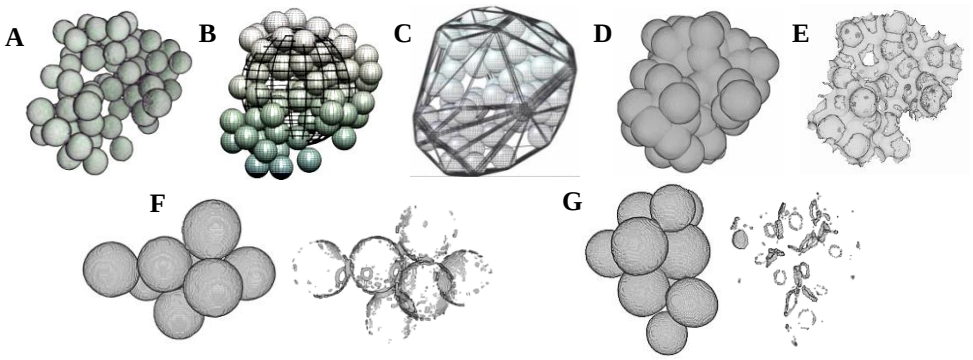
In order to enhance or control properties of aggregates and be able to predict the structure of final products, it is essential to establish a link between the product properties and the operating conditions. Experimental investigations have been conducted on agglomerates produced in spray fluidized beds using different primary materials (porous, non-porous) and HPMC (Hydroxypropylmethylcellulose) as the binder, under varying operating conditions, e.g. inlet gas temperature, binder spray rate and binder concentration.

X-ray µ-computer tomography, µ-CT, was utilized to evaluate the three dimensional micro-structure of the agglomerates and spatial distribution of each constituent primary particle in the aggregate. By performing sequences of image processing operations on volume images of the agglomerate matrices -- numbering every primary particle in the considered agglomerate and storing the coordination position of its centre, its radius and its volume -- were created. Based on this data, additional codes were developed to analyze particle positions in space and investigate the following morphological descriptors: radius of gyration, porosity, fractal dimension and pre-factor, coordination number distribution, radial distribution of particle position and porosity, and distributions of angles connecting every primary particle to its associated neighbours. By image analysis from volume images of the agglomerate, the binder could be distinguished from the primary particles. Thus, the local distribution of droplets on the particle surface and binder thickness could be analysed. Internal voids and the true internal morphology of the agglomerate were visualized and void size distributions were calculated as well. In addition formation of hollow solidified bridges and its dependence on drying temperature and binder viscosity were studied qualitatively.



A-Volume image of agglomerate. B-Idealized Matlab reproduction of agglomerate and gyration radius. C-Convex hull. D-Dilation. E-Matrix structure of internal voids. F-Porous primary particles and extracted binder. G-Non-Porous particles and extracted binder.

49. SIMULATING THE SPRAY FLUIDIZED BED GRANULATION BY MODELING THE AGGREGATION EFFICIENCY

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Monte-Carlo methods are a powerful tool to simulate complex particulate processes (such as fluidized bed agglomeration) by taking into account many (or all) micro processes that can possibly affect the net (macro) behavior of the system, but are still not applicable on an industrial scale due to their computational cost and stochastic nature. In this work we modeled the time dependency of aggregation kernel by observing the Constant Number Monte-Carlo (CNMC) simulation of the size independent aggregation process in a spray fluidized bed, under some simplifications. Micro processes like collision of particles, binder droplet deposition, rewetting of particles and drying of droplets are included in the Monte-Carlo simulation and hence modeled in the aggregation kernel to incorporate the possible effects of these micro processes on the aggregation rate. Furthermore, a complete new set of population balance equations is written for the parameters being identified as responsible for the time dependency of aggregation efficiency, namely total number of wet particles and total number of particles, by observing their birth and death rates including the effect of drying in the Monte-Carlo simulation. The other indentified parameters, explicitly, average wet surface fraction and success fraction of dissipation of kinetic energy, are extracted from Monte-Carlo results. These extracted parameters are then utilized in the developed set of population balance equations which is then solved numerically along with the expression of aggregation efficiency and conventional population balance equation for 1-dimensional pure agglomeration. For validation, the predicted results of our developed technique, such as total number of particles, total number of particles, aggregation efficiency and particle size distribution are then compared with the results of the Monte-Carlo simulation and found in good agreement.

55. A GENERAL FRAMEWORK FOR MODELLING THE DEFORMATION OF A BODY SUBJECT TO A LARGE NUMBER OF IMPACTS WITH SPECIAL REFERENCE TO SPHERONISATION

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We present a general mathematical framework for modelling the deformation of a deformable body when subject to a large number of successive impacts. The key element of the proposed approach is the contact law which determines the deformation of a sphere impacting with a rigid surface. The algorithm consists of creating an equivalent sphere for the deforming body, applying the contact law followed by an evolution law, which describes how the local contact flattening changes the shape of the body during successive impacts. A parametric study was performed to illustrate the effects of key material properties (which determine the contact law) and processing parameters (which determine impact velocity and location). The application of the model is illustrated for the process of spheronisation (rounding of soft cylindrical bodies into spheroids). It is shown that random impacts do not result in spheronisation, however, the impact conditions in specific particulate flow fields (such as the so-called "roping regime" present in spheronisation) can produce spheronisation. The underlying assumptions are discussed to highlight the current limitations and possibilities for exploitation for material design and process development for spheronisation and other granulation processes.

56. A COMBINED EXPERIMENTAL AND COMPUTATIONAL ANALYSIS OF THE EFFECT OF POWDER AND GRANULE PROPERTIES ON TABLET COMPACTION CHARACTERISITICS

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A mechanistic understanding of the correlation between the properties of the primary powder and granules, and their effect on tablet compaction characteristics can lead to enhanced and efficient process development in tablet manufacturing via high-shear wet granulation (HSWG), which is currently the most common route undertaken. Moreover, Quality-by-Design (QbD) in pharmaceutical manufacturing necessitates the identification of an optimal design space of critical quality attributes (CQAs) as a function of critical process variables and material properties. This study looks at the effect of power and granule properties on downstream tablet properties with the aim to optimize product quality within the generated design space and identify corresponding optimal HSWG operating conditions and material properties.

In this work, a design of experiment (DOE) approach has been employed and is a full factorial 3x3x3 DOE which explores the design space to identify the optimal values of 1) binder content, 2) wet massing time and 3) vessel RPM. The formulation comprises of acetaminophen and microcrystalline cellulose (30% APAP, w/w). Water is used as a binder. The resultant granules are dried and characterized to obtain distributions with respect to particle size (laser diffraction), porosity (pycometry) and content uniformity (XMT), which are key variables to account for in pharmaceutical granulation [1]. A sample of the granule mixture is also milled, mixed with a lubricant (MgSt) and compacted in tablet press simulator (Presster, MCC). CQAs for tablet compaction that are measured are tablet hardness (Pharmatron) and tablet dissolution (USP). Operating conditions for the tablet compaction process are constant in this study.

A novel multi-dimensional multi-component population balance model (PBM) with mechanistic kernels is developed and combined with semi-empirical models of the tablet compaction (Heckel) and dissolution (convection-diffusion). The models are then validated and statistically checked with a subset of available experimental data. Thereafter the model is utilized to *predict* granule and tablet properties and cross-validated with the unused experimental data. The models are fine-tuned as needed. Thereafter, the integrated model is utilized for process optimization (sequential quadratic programming) to identify optimal operating conditions and material properties that lead to specific product quality (i.e., desired tablet hardness and dissolution rate).

[1] P. Pandey, J. Tao, A. Chaudhury, R. Ramachandra, J. Gao, D. Bindra. A combined experimental and modeling approach to study the effects of high-shear wet granulation process parameters on granule characteristics. Pharmaceutical Development & Technology, (2012), 1-15.

57. LABORATORY SCALE GRANULATION OF OIL SHALE ASHES

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The power and heat production in Estonia is based over 90% on the combustion of local solid fossil fuel – Estonian oil shale (OS). The annual amount of ashes formed at that is on the level of 5-6 million tons. During combustion the inorganic part of OS undergoes a number of transformations including decomposition of carbonates with formation of calcium and magnesium oxides. Partially, these oxides remain in the form of free oxides causing the alkalinity of this waste. Reuse of ashes is currently very limited – only ~5%, mostly in the cement industry and in the production of building blocks. One promising possibility for large-scale utilization of alkali ashes is the liming of acidic soils. In Estonia there is 200 000 ha of agricultural land that needs permanent annual liming. Hence, the aim of current work was to study the possibilities of granulation of oil shale ashes for obtaining granulated product suitable for use in neutralizing of acidic soils exploiting at that present-day agricultural technique.

The ash samples studied were an ash mix from circulated fluidized bed combustion of OS (bottom, intrex, economizer and air pre-heater ashes collected and immixed in silo) and cyclone ash from pulverized firing of OS in Estonian Power Plant (PP). Samples were analyzed using chemical, grain-size, quantitative XRD, SEM and BET methods. The ashes studied differed in their chemical and mineralogical composition as well as in grain-size and specific surface area (SSA).

Granulation of ashes was carried out on a plate-type granulator with diameter 0.55 m using ash transportation water from Estonian PP. In addition, "black liqueur" and lignosulfonate from pulp and paper industry as well as water-glass and polyacrylamide aqueous solutions were used as the binding agents. Clay and cement clinker dust from SC Kunda Nordic Cement were used as solid binding additives to improve the properties of granulated oil shale ash. After granulation the moisture content of granules was determined and the size distribution analysis of the granules formed was performed with dried granules. Granules were tested for mechanical hardness using compression testing equipment and for durability on transportation, handling and storing by vibrosieve processing of granules. The behaviour of granules in soil was tested on the moisture level of 40% and 60% of the maximum moister capacity of soil and the leachability of ash components (Ca, Mg, Na, K ands S) in water was determined. The surface observations of the cross-section of granules were carried out with a scanning electron microscope Jeol JMS-8404, BET SSA analysis with a Sorptometer Kelvin 1042 and porosity measurements of granules with a Porosimeter Quantachrome Instruments PM-60-17.

The results obtained revealed that using the optimum amounts of solid binding additives and liquid binders and optimum drying regime enables to obtain granules resistant to pressure strength up to 20 N per granule and resisting 60 minutes of vibrational processing during which the formation of fines was less than 3-5%. The granules obtained had at that good solubility characteristics in aqueous media.

60. INVESTIGATION OF RATE-LIMITING STEPS DURING GRANULATION WITH CHEMICALLY REACTIVE BINDER

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Binders used in wet granulation can be grouped according to the mechanism by which they solidify as either solution binders (e.g. aqueous solutions of polymers such as PVP or HPC, or water itself), melt binders, and reactive binders. While the kinetics of binder setting in the former two cases can to some extent be controlled by the process parameters (drying rate or cooling rate), in the reactive case the rate of phase change is more or less spontaneous and driven by the kinetics of local reaction-diffusion processes near the binder-particle interface. Investigation of granulation-related phenomena such as binder spreading, particle collisions, nucleation and granule growth are thus further complicated by the simultaneously occurring chemical reaction and the change of physico-chemical properties of the binder that are associated with it. A two-way coupling exists between granulation and reaction kinetics: the evolving structure of the granules being formed influences the solid-liquid contact area to which the overall reaction rate is proportional, and the reaction influences the viscosity and other properties of the binder, which control its spreading on primary particles and ability to dissipate the kinetic energy of inter-particle impacts.

The system of dodecyl-benzenesulfonic acid as a binder and sodium carbonate powder as primary particles is considered in this work [1,2], motivated by the so-called dry neutralisation process used in the manufacture of powder detergents. The measurement of dry neutralization kinetics in a laboratory-scale mechanically agitated granulator is described. The volume of evolved carbon dioxide, which is a by–product of the neutralisation reaction, has been used for following the reaction kinetics, and the effect several parameters on the progress of the reaction has been investigated. The parameters include process temperature, agitation rate, size distribution (thus specific surface) of the primary particles, and the mode of binder addition (step-wise addition). The overall conversion of the reaction and the properties of the formed granules (size distribution, internal structure and porosity) have been evaluated in each case. A mathematical model of the process has been formulated and used for testing hypotheses about the rate-limiting steps in each stage of the process, which can be rate of binder spreading, the availability of fresh solid surfaces, the diffusion rate of reaction components near the interface, or the intrinsic reaction kinetics. Knowlege of the rate-limiting steps then serves for making rational process control decisions.

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[2] M. Schöngut, D. Smrčka, F. Štěpánek, Experimental and theoretical investigation of the reactive granulation of sodium carbonate with dodecyl-benzenesulfonic acid, Chem. Eng. Sci., (2012) *in press*.

61. USE OF REACTIVE WETTING AS A TOOL FOR REAL-TIME MONITORING OF BINDER DISTRIBUTION DURING GRANULATION

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The distribution of binder among primary particles is a key elementary process that occurs during wet granulation and ultimately determines the properties of granules such as their size distribution or porosity [1]. The kinetics of binder spreading can be observed in macroscopic systems such as a powder bed or a compacted pellet, or microscopically e.g. on a single primary particle. However, the direct observation of binder spreading on primary particles and within the porous structure of growing granules under real process conditions is not feasible. Only indirect information about the binder distribution can be obtained ex-post by analysing the granule internal microstrucure [2]. However, it has been shown recently [3] that in the case of reactive granulation, where a chemical reaction occurs at the interface between the primary particles and the binder, monitoring the progress of the chemical reaction can be used as a surrogate for indirectly measuring the binder-solid contact area, and thus the spreading kinetics. To do this, two conditions have to be met: 1) the relationship between the solid-liquid contact area and the apparent reaction rate has to be known or independently measurable; 2) the progress of the chemical reaction has to be observable in real time by a suitable physical or analytical method.

In the present work, the methodology is demonstrated using a model system consisting of two substances - sodium carbonate as primary particles and a saturated solution of citric acid as a binder (with or without additional polymeric components to increase viscosity). Upon contact between these two components, the neutralization reaction gives rise to a carbon dioxide gas, whose quantity can then be measured e.g. volumetrically. In the first step of this experimental study, reaction rate constants were determined using a reaction of a known amount of narrow-sized sodium carbonate particles with an excess of citric acid solution to ensure complete wetting and thus known and constant contact area. Carbon dioxide volumetric curves were obtained as a function of time. Viscosity of the acid solution was adjusted using commonly used polymeric binders (PVP, HPC). The second phase of the study focused on granulation experiments in a mechanically agitated cylindrical vessel. The release rate of carbon dioxide was again measured and its values were converted to the binder-solid contact area using previously determined reaction kinetics. The terminal contact area was then verified using x-ray computational tomography of the formed granules.

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[3] M. Schöngut, D. Smrčka, F. Štěpánek, Experimental and theoretical investigation of the reactive granulation of sodium carbonate with dodecyl-benzenesulfonic acid, Chem. Eng. Sci., (2012) *in press.*

62. PREMEDITATED MATERIAL BREAKAGE DURING GRANULATION: SCREW DESIGN AND PRODUCT QUALITY CONSIDERATIONS

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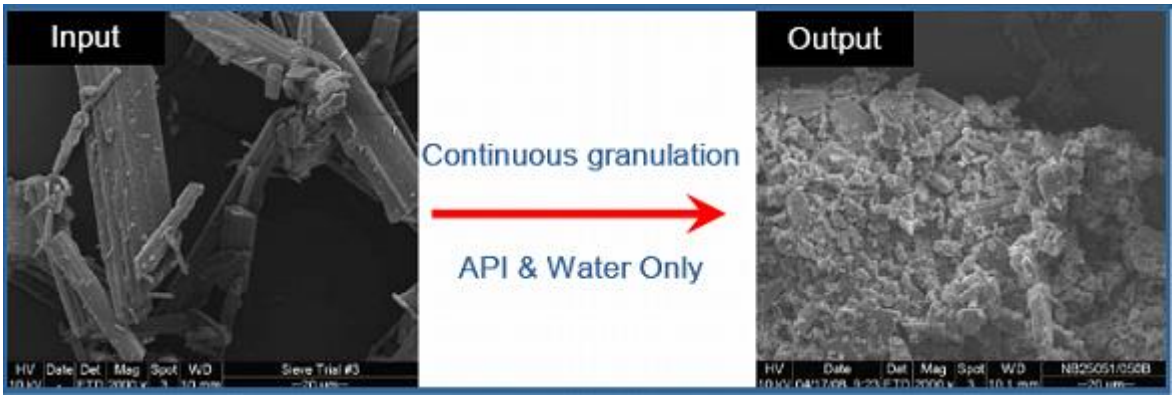
A clear understanding of the fundamental material transformations is critical to determine the appropriate equipment setup and processing parameters to deliver a high quality product. Using twin screw continuous wet granulation, there is an opportunity to customize these material transformations to maximize robustness and product quality.

In this work, we demonstrate the utility of leveraging the flexibility of the granulator screw design to go beyond the standard goal of creating a suitable granule for downstream processing (e.g. flow/density improvements, etc.). The screw design intentionally caused input material breakage while agglomerating the material to create final granule. This allowed a wider variety of input materials to be used yet the output material was extremely consistent. The advantages and disadvantages of this type of granulation approach are discussed in term of product quality and regulatory considerations.



Scanning electron microscopy images of input api (active pharmaceutical ingredient) and the output "granulated api"

63. THE RHEOLOGY OF DENSE GRANULAR FLOWS IN A DISC IMPELLER HIGH SHEAR GRANULATOR

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High Shear Granulation (HSG) is a very common process with a wide variety of applications. Prior to any phenomena happening in such systems like agglomeration, breakage, etc. an understanding of the flow pattern is required. The study of flow in dense granular flows is much more complicated than regular fluid flows, since particle assemblies exhibit a mixture of both fluid and solid characteristics.

In this study, HSG in a Disc Impeller granulator is explored. The equipment is similar to the system used by Reynolds et al [1]. The particle flow in this dense system is mostly governed by long-lasting multi body contacts and frictional sliding between particles. Hence, the assumptions of the kinetic theory of granular flow (KTGF), in particular instantaneous binary collisions, are not fulfilled [2]. Recently, a new continuum approach to dense granular flows by treating it as a non Newtonian fluid, was proposed by Jop et al [3]. This approach has been found very attractive because of its simplicity and accuracy. Besides, the computational load is much lower than in other continuum approaches as well as DEM. Therefore, the aforementioned model is used to simulate the flow behaviour in the present work.

Experiments were performed at different impeller speeds and solids loading, the torque was measured and particle velocities near the wall were obtained using high speed camera and PIV analyses. An interesting observation was a maximum torque exerted on the system at intermediate impeller speeds. The particle bed is expanded at this point and particle agitation is vigorous. From the PIV analysis it is clear that the particulate phase exhibit partial slip behaviour at the walls.

CFD simulations, using the non Newtonian rheology model, are performed on the described system. Initially a no-slip condition for the particulate phase was used. The overall flow field looks reasonable. The simulation results show somewhat higher torque values than in the experiments and does not give a maximum in the torque. We are presently implementing partial slip into the code.

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65. INFLUENCE OF RAW MATERIAL PROPERTIES UPON CRITICAL QUALITY ATTRIBUTES OF CONTINUOUSLY PRODUCED GRANULES

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Recently the interest has arisen in the pharmaceutical industry to shift its manufacturing of solid dosage forms from traditional batch production towards continuous production. The main reasons for this change are avoiding scale-up issues, reducing cycle times, variability and production costs, ensuring faster product release, increasing flexibility and efficiency, and improving product quality. Traditionally, the end product quality is evaluated by means of off-line and time-consuming analysis. It is clear that these off-line tests would annul the advantages of continuous processing. The International Conference of Harmonisation (ICH) states in Q8 'Pharmaceutical Development' guideline that the manufacturer of pharmaceuticals should have an enhanced knowledge of the product performance over a range of raw material attributes, manufacturing process options and process parameters. This approach fits further into the Process Analytical Technology (PAT) and Quality by Design (QbD) framework, as launched by the Food and Drug Administration (FDA).

The present study evaluates the effect of chemical and physical variability of raw material properties (e.g., particle size, flowability,...) on the quality attributes of granules and tablets, produced via a continuous from-powder-to-tablet wet granulation line (ConsiGma^{TM}-25, GEA Pharma Systems, Belgium). In first instance, the granulation process parameters were kept constant to examine the differences in the end product quality caused by the different properties of the raw materials. Secondly, the gained knowledge on how the examined raw material properties influence the quality of the end-product is used to further study how the granulation process parameters need to be set as function of the properties of the raw materials, hence ensuring the desired properties of the end-product at all times.

Theophylline–Lactose–PVP (30-67.5-2.5%) was used as model formulation, with distilled water as granulation liquid. Seven grades of theophylline, differing in particle size distribution (D50 varied between 8 and 60 µm), bulk densities (0.3-0.5 g/mL), flowability (from not flowing to very cohesive according to a ring shear tester), were granulated. The granules were characterized regarding size distribution, content uniformity, density, friability, theophylline solid state and moisture content. Furthermore, the tensile strength, disintegration and friability of their consecutively produced tablets were evaluated. A second model formulation, examining different grades of microcrystalline cellulose (MCC) was evaluated similarly.

The results show that differences in raw material properties both affect their processability, as such (e.g. torque during granulation) and the quality attributes of the resulting granules and tablets. Granules differ in density and particle and size distribution (smaller start material results in more fines) for example, whereas tablets differ in tensile strength and flowability.

72. MULTI-DIMENSIONAL POPULATION BALANCE MODEL DEVELOPMENT AND VALIDATION FOR A TWIN SCREW GRANULATION PROCESS

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Wet granulation processes are often used in tablet manufacturing. Although these processes are typically operated in batch mode, continuous pharmaceutical processing has demonstrated potential advantages in cost, scalability, and controllability. Twin screw granulation (TSG) is particularly suitable for this application because of its design flexibility, short residence time, and ability to mix multiple ingredients [1]. Process validation is essential in the highly-regulated pharmaceutical industry, and the proposed modeling and experimental approach undertaken in this study, is well suited toward implementing QbD in pharmaceutical manufacturing processes.

Population balance models (PBM) can be used to simulate powder processes by tracking the number of particles with a given set of attributes over time. Typically, one-dimensional PBMs are implemented, considering particle size as the only important attribute. These models have significant limitations because rate processes often depend on other attributes, such as composition, porosity, and liquid content. For example, a poor liquid distribution can result in variations in liquid content and a wider particle size distribution. Additionally, particle composition is of particular importance in pharmaceutical granulation since inhomogeneities can result in variations in the final product dosage form.

In this study, a novel multi-component PBM for the TSG process was developed, taking into account the rate processes of aggregation, breakage, liquid addition, and consolidation. Interactions between multiple solid components (e.g. active and excipient) and the amount of liquid were accounted for in quantifying the aggregation and breakage rates. Multi-scale information was also incorporated into the PBM in the form of particle fluxes as a function of radial and axial position. Fluxes in this study were obtained from theoretical correlations. On-going work involves the coupling of DEM simulations with the PBM where the DEM is utilized to obtain for more accurate particle collision frequencies and velocities, particularly with respect to screw configuration.

Experimental data was obtained for the TSG process, whereby the effect of initial particle size distribution and liquid-to-solids ration on key granule properties was studied. The data was used to estimate adjustable parameters in the proposed mechanistic kernels and to validate the overall process model. The simulation results showed a good agreement with experimental data. Finally, the validated model was used to optimize granule properties and to identify the optimal operating conditions (RPM, L/S ratio) and material properties (initial PSD) of the TSG process.

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73. CFD SIMULATION OF TRANSIENT PARTICLE MIXING IN A HIGH SHEAR MIXER

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Particle mixing is a key operation in pharmaceutical processing. In this work, the Eulerian-Eulerian multiphase framework has been employed to model and simulate the particle flow and mixing behaviour in the formulation of dry powder for inhalation. The kinetic theory of granular flow and frictional stress models are used to close the transport equation of particle flow with high solid volume fraction in a high shear mixer [1]. The mixing behaviour within the mixer is tracked by adding a scalar transport equation for the tracer that follows the transient state of particle flow. The solid velocity profile at the wall is experimentally validated by using high speed camera and PIV evaluation. Different feeding positions of scalar are investigated and the dynamic of mixing is experimentally tracked by imaging technique which is processed in Matlab image toolbox to obtain tracer concentration profile. The model can capture main features in the granular flow motion, e.g. bed height and dominating flow direction. Quantitative comparisons prove that tracer concentration is over-predicted whilst mixing degree and mixing time is in agreement with experimental data. The results show that further development of the continuum kinetic-frictional based models is needed. However, without limitation in scale of mixer and particle load, the model with addition of tracer can be used to predict the particle mixing behaviour at large scale.

Keywords: Particle mixing, Kinetic theory of granular flow; Frictional stress models; Multiphase flow.

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75. CO-PROCESSING PHARMACEUTICAL INGREDIENTS TO ENGINEER A NOVEL MULTIFUNCTIONAL BINDER

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The objectives of the present study were to prepare and characterize a spray dried fine particulate binder compromising a binder, polyvinylpyrrolidone (PVP), and a lubricant material, L-leucine (PVP-Leu), and evaluate its unusual combined binder efficiency and glidant potential. Commercial grade PVP and PVP spray dried without leucine (PVP-SD) were used as controls. The binders were characterized by particle size, cohesion and flowability. Acetaminophen was chosen as a model poorly-compressible high-dose drug and was blended with the binders using a low-shear mixer. The glidant action of the PVP-Leu was evaluated using bulk density and angle of repose (AoR). Tablets were prepared by direct compression and hardness was determined as an indicator of binder efficiency. The mean particles size of PVP, PVP-SD and PVP-Leu was 68.6 ±0.6, 2.9 ±0.06 and 3.1 ±0.07 µm, respectively. It was observed that the PVP-Leu demonstrated significantly lower cohesion and improved flowability compared to PVP-SD. It was also noted that acetaminophen exhibited low bulk density and high AoR indicating poor flowability. The results indicated that PVP-Leu could increase the bulk density and reduce the AoR of acetaminophen after blending. The results also indicated that the hardness with PVP and PVP-Leu was same, whereas, PVP-SD imparted twofold higher hardness to tablets. Thus, the PVP-Leu combination exhibited both good binding ability and glidant action and represents an attractive potential multifunctional excipient for direct compression of high dose drugs.

76. COMPARISON BETWEEN GRANULES PRODUCED BY SPRAY DRYING AND DRY GRANULATION FOR THE FABRICATION OF CERAMIC PORCELAIN TILES

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Traditionally granules produced by spray drying are used in the fabrication of ceramic tiles because they provide the uniform filling of the pressing moulds. During compaction, a subsequent part of the process, these granules shall plastically deform to eliminate the intergranular pores, increase the mechanical strength of the compact and develop required shape and dimensions.

The growing concern with energy and environmental issues in recent years has encouraged the search for other granulation processes that would require less energy and would be more environmentally friendly. In this scenario the dry granulation seems to be a very promising alternative. From the literature and industrial practice in other segments it's a well known fact that the shape and size of the granules produced by dry granulation can be similar to those produced by spray drying. So, the uniform filling of the moulds should not be a problem. However, there is very little in the literature regarding the plastic deformation of the granules produced by dry granulation related to the fabrication of porcelain tiles.

In this context the objectives of this study were: 1) to adjust the dry granulation process to obtain granules with size and shape similar to an industrial powder produced by spray drying; 2) to comparatively evaluate the mechanical behavior of granules obtained by spray drying and dry granulation, during compaction and 3) to look for adjustments of the dry granulation process that would produce granules with plastic deformation similar the spray dried granules.

To achieve these objectives two granulated powders, with the same chemical and mineralogical compositions, typical of glazed porcelain tiles, were used – an industrial spray dried and a dry granulated powder. The size distribution, shape and flowability of the granules produced by spray drying and dry granulation were similar. However, the bulk density of the granules obtained by dry granulation was significantly higher. As a consequence, the yield strength of the dry granulated powder was higher and the compacts, pressed under the same conditions (industrial conditions), exhibited higher porosity and larger pores. These differences profoundly influenced the behavior of the compact during fabrication and the characteristics of the final product.

Based on the understanding of the role of the raw materials that constitutes the porcelain tile composition and the dry granulation process, new granulation conditions, which resulted in granules with lower yield strength, were established. The compacts obtained with these granules, using industrial pressing conditions, presented porosity and pore sizes similar to those obtained with spray dried powders.

78. NEW GRANULATION PROCESS OF INTERMETALLIC COMPOUND OF BERYLLIUM FOR FUSION APPLICATION

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Tritium needed as a fuel for fusion reactors is produced in the fusion blanket region by neutron capture reaction of lithium-6 (^{6}Li). Neutron multiplier is required for adequate tritium breeding in the blanket of fusion reactors. Pure beryllium metal (Be) is one of the candidate materials for neutron multipliers in the fusion blanket. However, some problems have been anticipated such as volumetric swelling and hydrogen generation reaction of Be in the demonstration fusion power (DEMO) reactors under high neutron flux and high temperature. Advanced neutron multipliers with lower swelling and higher stability at high temperature are desired in pebble-bed blankets, which would have a big impact on the design of a DEMO reactor, especially on the blanket operating temperature.

In parallel to the ITER program, Broader Approach (BA) activities are being implemented by the EU and Japan, aiming at early realization of the fusion energy. Beryllium intermetallic compound (beryllide) such as $Be_{12}Ti$ is candidates of the advanced neutron multipliers because beryllide has good potential under higher temperature more than Be. Based on the common interests of the EU and Japan in DEMO, R&D on beryllide are carried out through the DEMO R&D of the International Fusion Energy Research Centre (IFERC) project as a part of the BA activities from 2007 to 2016. This activity has the objective of development of granulation technique of beryllide and its characterization.

In order to fabricate the beryllide pebbles, a rotating electrode method was selected because this method has a lot of experience not only for Be pebble fabrication but also for metallic pebble fabrication in the general industry. For granulation by the rotating electrode method, beryllide with shape of rod is necessary as raw material electrode. As conventional methods, a powder metallurgy process including a hot isostatic pressing method, a casting method and an arc-melting method have been proposed for beryllide synthesis. However, beryllide is too brittle for the fabrication of rods by these methods. And, it was clarified that these methods had some problems such as its complicated process, time-consuming characteristics and difficulty in composition control.

A plasma sintering method has been proposed as new technique that uses a non conventional consolidation process, because this method is simple, and is easy to control. And, this method results in powder surface activation that enhances powder particle sinterability and reduces high temperature exposure. From the results of beryllide synthesis experiments, it was clarified that the beryllide could be simultaneously synthesized and jointed by the plasma sintering method. Beryllide rod of $Be_{12}Ti$ has been successfully fabricated by the plasma sintering method.

Using this plasma-sintered beryllide rod, prototype pebble of beryllide was performed by the rotating electrode method. From the results of beryllide granulation experiments, the prototype pebbles of $Be_{12}Ti$ with 1 mm in average diameter were successfully fabricated. The present paper describes new granulation process of beryllide using these methods including the optimization results of granulation conditions.

80. GRANULATION OF ULTRA-FINE POWDERS: TRACKING CHANGES IN GRANULAR MICROSTRUCTURE USING XRCT

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Many granulated products used in consumer goods, agricultural chemicals, pigments, and specialty chemicals are made from ultrafine primary particles (0.1-10 μm). However, the granulation behaviour of ultra-fine powders is poorly understood. These materials are known to naturally aggregate, potentially leading to complicated microstructures which are strongly dependent on the history of the powders prior to granulation. In order to predict the final granule properties, it is important to understand how this microstructure changes during granulation.

In this work, the changes in the granular microstructure during consolidation (densification) are tracked as a function of the granulation time using X-Ray Computed Tomography (XRCT). Single-droplet granules are formed and then tumbled up to one hour with additional dry powder to prevent coalescence. The dry powder is observed to layer onto the outside of the seed granules. This gives the granules a complex core-shell structure in which the core is made up of a series of small aggregates with macropores between the aggregates in the core. It takes many minutes for the aggregate structure in the core to disappear. XRCT of the granules sampled every few minutes allows for quantitative tracking of changes in the granular microstructure, including the thickness of the powder layer as the granules densify, average porosity and pore size distribution, and various stereological descriptors. Ultra fine zinc oxide and titanium dioxide are used as model powders with water and silicon oils of varying viscosity as model liquids. The stress-strain history of the dry powder bed prior to granule formation is also varied to examine its effects upon the granule microstructure development. The effect of formulation properties and powder bed history on the kinetics of granule microstructure development are presented. Implications for modelling the development of granulation of ultrafine powders, as well as for optimizing the granulation processes, are discussed.

81. UPGRADING THE CRUSH STRENGTH OF AMMONIUM NITRATE PRILLS BY COATING WITH LIMESTONE OR DOLOMITE POWDER

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Calcium ammonium nitrate (CAN) is usually produced by prilling of premixed concentrated solution of ammonium nitrate (AN) with powdered limestone [1]. We presume that it is also possible to produce CAN prills by coating AN prills with powdered limestone or dolomite instead of mixing it. Coating is also aimed to increase the prills in size in order to achieve better miscibility with the other fertilizers. Considering thermal instability of AN as shown in [2, 3] it was found that AN prills coated with limestone or dolomite powder were thermally as stable as AN blends with limestone or dolomite. Thereby, crush strength of granule is an important characteristic considering storage, transport and distribution of granular fertilizer. Linkage between the amount of binder used in the coating process and product quality (fractional composition, crush strength, nitrogen content, etc.) was under investigation.

Commercial fertilizer-grade AN (Tserepovetski Azot Ltd, prill's size 2-2.5 mm) was coated with different Estonian limestone and dolomite samples ground to a particle size <45 μm using saturated solution of AN as the binding agent. The experiments were carried out on a laboratory pan-type granulator with a diameter of 0.55 m, angle of inclination between 30-45° and rotation speed 23 or 28 rpm.

One of the reasons of low durability of neat AN prills on compression is the presence of voids inside the prills. Coating of the AN prills allows to increase durability of prills on the account of durability of the cover. The results of crush strength measurements proved that strength of coated prills exceeded that of neat AN prills 3–4 times – 10-16 N for coated prills instead 3-4 N for neat AN prills. The yield of coated prills with diameter 2 - 4 mm reached up to 90%.

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82. CONTINUUM MODELING OF PARTICLE FLOWS IN HIGH SHEAR GRANULATION

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High shear granulation (HSG) is a common process in pharmaceutical industry. A better understanding of the flow conditions of powders and granulates in large scale HSG equipment is crucial for constructing predictive models. The staggering amount of particles in the process makes the use of continuum flow models highly attractive. This article discusses the possibilities and problems in using continuum modelling in HSG systems and evaluates some of the available modelling approaches.

We examine several dense granular flow models studying both underlying theory and how they perform in practice. The studied models are the frictional model by Shaeffer [1], modifications to the transport coefficients describing the solid phase stresses similar to those used in Khain and Meerson [2] and the framework developed by Jop et.al. [3] using a depth averaged flow model for constant solid volume fraction flows.

The model by Shaeffer has previously been used with the conclusion that the solid phase stresses are underestimated [4]. We show theoretically and in practice that this approach is not appropriate due to a strong resolution dependence of the model. The approach taken by Khain and Meerson, among others, to try to modify expressions from rapid granular flow to be valid also in the dense region is attractive from a theoretical point of view. Making use of the rigorous framework of kinetic theory, the applicability of a number of such models to HSG will be evaluated. The modelling framework derived by Jop et.al was used in a disc impeller HSG equipment. The results show that the model can well predict the behaviour of the solid phase viscosity for the dense granular flow. The model is still restricted to constant volume fraction flows and needs to be expanded to include a varying volume fraction.

We conclude in this paper that continuum modelling of HSG has a promising outlook but there is a need to develop better models for the dense regions of the flow. We also give and evaluate some of the available options to treat these regions.

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83. FLUIDIZED BED MICRO-ENCAPSULATION OF PROBIOTIC MICROORGANISMS FOR ANIMAL FEEDING

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Functional ingredients are not only of high relevance in the food industry, but also for animal feeding. Functional ingredients with high nutrient value as well as probiotic strains can support animal health and prevent infections or malnutrition. Lactic acid bacteria are one of the most important group of probiotic microorganisms, but it is also possible to apply yeasts or spores of Bacillus strains in probiotic products. Freeze drying is often used for stabilization of starter and probiotic cultures, but requires considerable drying time, investment and energy costs.

The work has focused on the development of a technique to encapsulate probiotic strains for piglet feed application. For this application it is required to achieve a targeted release within the gastro-intestinal tract and stabilize the encapsulated material against pH stress. A sufficient oxygen barrier, light stability and low hygroscopicity are required. In addition, a simple and robust application has to be guaranteed by suitable product parameters such as concentration, particle size, bulk density and dumping angle. Last but not least, product costs need to allow an application in feed industry.

The applicability of a micro-encapsulation and drying based on a fluidized bed process has been evaluated on a flexible mobile laboratory plant. This semi-discontinuous plant is called “minibatch” with a flow capacity up to 0.5 kg per hour. Suspensions of probiotic bacteria like Lactobacillus farciminis, Saccharomyces cerevisiae and Bacillus subtilis have been granulated in combination with different primary powder. Maltodextrin, sugars, milk and whey proteins as well as modified starches have been used as primary matrix, also in combination. The impact of liquid and solid material input, dry matter, air flow and supply air temperature less than 100 °C on encapsulation and drying efficiency as well as probiotic strain activity has been evaluated. It is important to protect the probiotic material to maintain the activity after drying, so the product temperature during the process should be not higher than 45 °C. Furthermore the legislation of the EU has to be considered, so the colony forming units per kilogram have to be obtained after the drying process. Suitable processing conditions have been identified to generate a stable product. Processing conditions and technical requirements will be discussed along with a discussion of possible applications in feed industry.

85. IMPLEMENTATION OF SMALL SCALE CONTINUOUS WET GRANULATION IN THE PHARMACEUTICAL INDUSTRY

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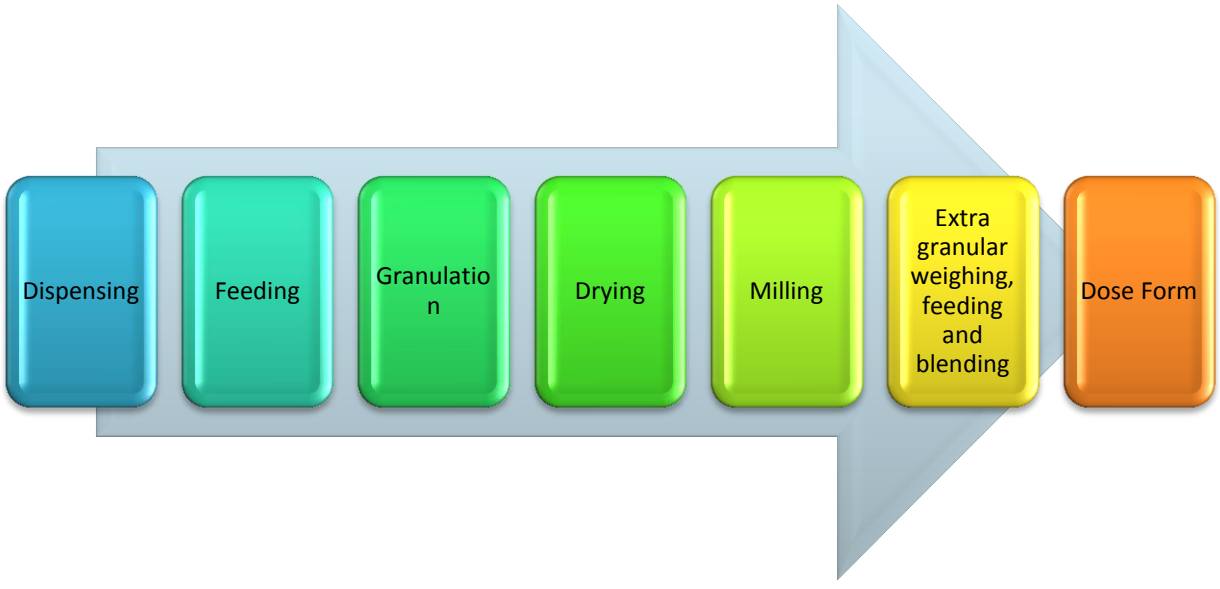
Continuous processing and in particular continuous wet granulation has received a high level of interest in recent years for the manufacture of pharmaceutical products. The key business drivers for this include reduction in scale up time and costs in the R+D stages as well as reductions in operating costs, work in progress and footprint during commercial manufacture.

Whilst continuous granulation is well known within a number of industries, this is generally for high volume, high throughput processes. Within the pharmaceutical industry, limitations on equipment capability have limited its use until recently when equipment of appropriate nature and scale has become available. In particular co-rotating twin screw equipment has been used for the wet granulation stages at typical rates of 1-40kg/hr and a number of articles have been published showing the effect of granulation parameters on granule properties.

In this work the broader process is considered and the actual implementation of the technology in a commercial R+D and manufacturing environment. Key limitations and considerations for raw material feeding, process limitations for control of granule composition, formulation development, the wet granulation step, the drying step and subsequent downstream processing are discussed. Implementation of PAT and process monitoring technologies are also demonstrated.



86. DISCRETE ELEMENT MODELLING OF ELASTIC BENDING OF CERAMIC-POLYMER BEAMS GENERATED BY SPOUTED BED SPRAY GRANULATION

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In view of mimicking the design principles of nature's biological materials, processing techniques involving spouted bed spray granulation are gaining importance for the synthesis of novel ceramic-polymer composite materials. For particle sizes in the µm-range, this technique can be used to generate large amounts of composite granules, whose substructure can be optimized for further processing to composite materials. The mechanical properties of such particulate reinforced composites depend on various parameters, such as filling degree, particle shape and sub-structure, the mechanical properties of the polymer, etc. While experimentally it can be tedious to study the influence of each parameter individually, simulation tools, such as the Discrete Element Method, can be used to gain insight into how the mentioned parameters influence the mechanical response of the final macroscopic material. Results of such mechanical tests are presented which highlight the role of the loading scheme and of some micromechanical parameters.

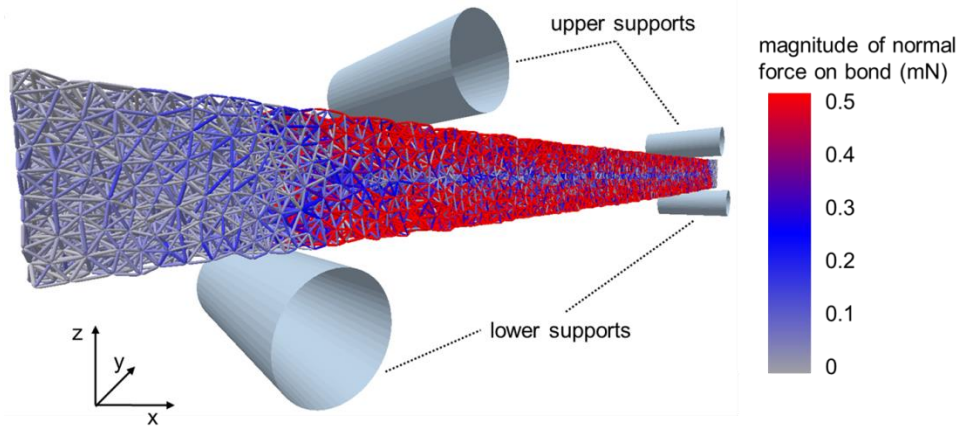

Figure 1: Magnitude of normal force acting on the solid bonds connecting the particles in the beam (particles not shown). The load is applied by the two upper supplies.

Acknowledgements: We gratefully acknowledge financial support from the German Research Foundation (DFG) via the collaborative research center SFB986 "M3", project A3 and A6, and the Cluster of Excellence "Integrated Materials Systems" within the Landesexzellenzinitiative Hamburg, Germany.

87. INFLUENCE OF INTERNAL STRUCTURE PARAMETERS AND ADDITIVES ON THE MECHANICAL PROPERTIES OF SPRAY DRIED GRANULES

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The fracture and deformation behaviour of ceramic spray dried granules has a decisive influence on the resulting product properties and can be influenced by the means of changed added additives like binders, dispersants or lubricants or by the modification of the internal granule structure. The structure itself can be modified by the spray drying conditions as well as the suspension formulation. For a specific optimization of the mechanical granule properties the correlations between structure and/or additives an resulting fracture and deformation behaviour has to be known.

Within this work, several granule samples were produced and characterized concerning their mechanical properties as well as internal granule structure using an alternative image analysing technique of prepared granule cross sections. For the structure characterisation parameters like average shell thickness, shell porosity (ε_{micro}) and total granule porosity were determined using image analysis software. The mechanical properties like fracture deformation and fracture force were determined using an uniaxial compression tester for single granules. From the results the influence of varied additives in comparison with modified internal structures on the resulting mechanical properties are evaluated: At comparable additive kind and amount, a reduced micro porosity leads to increased fracture force and stiffness. Also an increase of shell thickness showed the same effect whereas the micro porosity surpasses the shell thickness and seems to be the decisive structure parameter. Comparing structures of granules produced from suspensions with different types of additives (binder, lubricant, ...), the resulting mechanical properties are mainly dependent of the amount and binding effect of the additive. The structure influence was overlaid by the physical properties of the additives for the investigated substances.

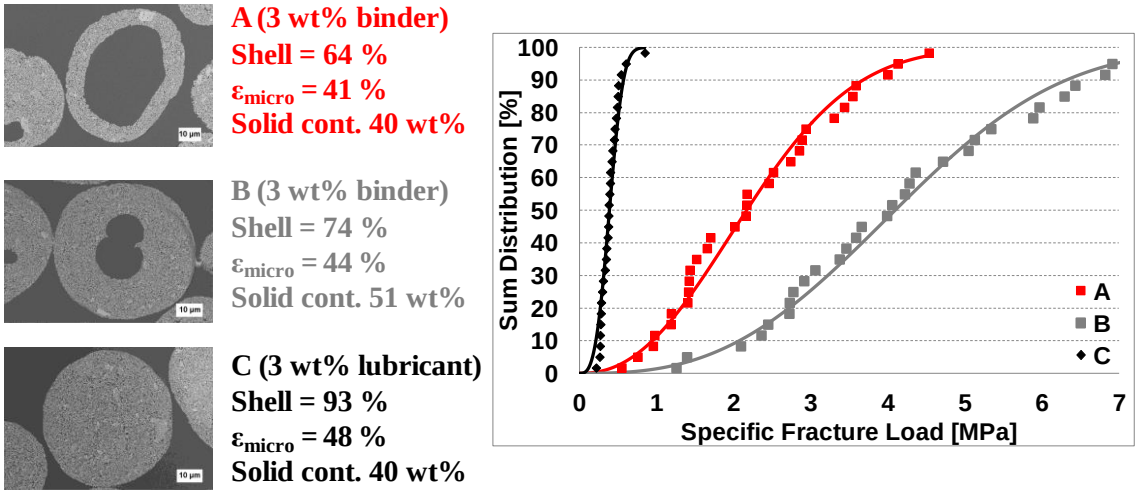

Figure 1: Effect of structure / additive on fracture load

90. ANALYSIS OF THE EFFECT OF IMPELLER TYPE AND SPEED ON THE RATE AND QUALITY OF MIXING IN A HIGH SHEAR MIXER

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In the pharmaceutical industry, product homogeneity is an extremely important factor in powder mixing due to the small scale of powder used per dose [1]. To increase product safety and consistency a very fine degree of mixing is desired, which is very difficult to achieve often due to the size, density and physical property differences of the powders used to create pharmaceutical formulations [2]. Flow patterns throughout many powder mixing technologies, particularly high shear/vertical axis mixers, are not well understood [3]. As such the determination of the best mixing conditions in a given vessel, including fill height, operating speed and mixing time is a purely trial-and-error approach and can be a time and financially costly process. A novel extension to a previous method using cohesive and free flowing lactose (white) and cohesive micronized iron oxide colouring agent (dark red) has been used to evaluate the extent and rate of mixing in a high shear mixer. Measuring the change in hue and intensity of micronized iron oxide in a lactose bulk enables the analysis of two distinct mixing behaviours, namely the de-agglomeration of the pigment (transition from red to orange) and the dispersion of a given sized aggregate through the bulk material (increase in the intensity of the blend's hue. In this study 99% lactose plus 1% iron oxide tracer were blended respectively to evaluate the extent of fine particle dispersion and de-agglomeration. A series of blends were manufactured in a single scale high shear mixer using four different impeller types and three impeller speeds which were selected to create different powder flow regimes. Blends were sampled at various time points at several regions of the powder mass and the blend colour was analysed. The change in blend colour with time showed how the impeller type and impeller speed affected the blend homogeneity and the rate of mixing for each process. This improved colour method will aide in the selection of appropriate blending equipment and processing conditions to achieve equivalent powder blends.

[1] B.H. Kaye, Powder mixing, Powder Technology Series, Chapman & Hall, London, (1997).

[2] P. Knight, Challenges in granulation technology, Powder Technology, 140 (3) (2004) 156-162.

[3] F. J. Muzzio, P. Robinson, C. Wightman, D. Brone, Sampling practices in powder blending, International Journal of Pharmaceuticals, 155 (1997) 153-178.

91. EFFECT OF ROLL COMPACTION ON DISINTEGRATION TIME AND DISSOLUTION RATE OF THEOPHYLLINE

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Theophylline is used in asthma therapy and classified as Class I drug according to Biopharmaceutics Classification System. It exists as monohydrate and two polymorphic forms of anhydrate (stable and metastable form). In contact with water Theophylline anhydrate form is converted to the hydrate form, which dehydrates to the metastable anhydrate during drying. The metastable anhydrate form of Theophylline has different properties in comparison to the stable anhydrate form, such as solubility and dissolution rate. Therefore wet granulation step in formulation development is not the first choice for Theophylline.

The aim of the study is to investigate the effect of roll compaction (dry granulation) on the dissolution rate and disintegration time of different Theophylline grades. Theophylline monohydrate, Theophylline anhydrate powder and Theophylline anhydrate fine powder (BASF ChemTrade GmbH, Germany) were used in order to check if there is any difference in compactibilty of different pseudopolymorphs and different particle size of the same polymorphs (anhydrate). The binary mixture of 0%, 10%, 30%, 50% and 100% Theophylline anhydrate powder, Theophylline anhydrate fine powder, Theophylline monohydrate and Cellulose Microcrystalline AVICEL PH 101 (FMC BioPolymer, USA) respectively were prepared by mixing the powders during 15 min in Turbula® mixer. Roll compaction of the mixtures were performed using a Fitzpatrick IR220 Chilsonator and subsequently milling of the ribbons with a L1A LabScale FitzMill.

Tablets of a total weight of 350 mg and 10 mm diameter were compressed using the constant gap of 3.2 mm with a Compaction simulator, MCC Presster®.

Influence of roll compaction and milling on the dissolution rate and disintegration time of Theophylline was analyzed by Dissolution Test Apparatus (Sotax AT 7, Sotax, Switzerland) and Tablet Disintegration Tester (Sotax DT 2 Automated Detection, Sotax, Switzerland).

The results of this study showed that roll compaction and milling has no influence on the polymorphic forms and compressibility of Theophylline.

92. IMPROVED CONTROL OF GRANULE PROPERTIES VIA "STEADY STATE" GRANULATION

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Industrial pharmaceutical high shear wet granulation processes generally adopt short granulation time with copious amount of liquid binder resulting in broad granule size distributions due to the difficulty in controlling this transient process. The “steady state” granulation approach [1] uses a slow liquid addition rate, vigorous mixing and extended wet massing to narrow the granule size distribution and reduce the polydispersity of granules. The steady state condition is achieved when the granule properties show no significant changes with an increase in wet massing time. The original study [1] produced a narrow size distribution of spherical granules. However, there have been no published follow-up studies.

We investigated the "steady state" granulation behaviour using a formulation of 63-73% lactose monohydrate, 20-30% microcrystalline cellulose, 3% HPC-EXF, 3% croscarmellose sodium and 1% Rhodamine B as the tracer in a 5 L high shear mixer using impeller speed of 245-505 rpm. Cooling water at 22°C was circulated through the bowl jacket to control the powder temperature. The liquid level was varied between 20-32% using a delivery rate of 2%/min (dry basis) followed up by 30 min of wet massing time. The granule size, shape and dissolution behaviour were characterized for each batch. Uniformity in granule size and shape was observed but over a narrower range of 27-30% liquid level, with irregularly shaped granules formed below 26% liquid level and broader granule size distributions produced above 30% liquid level due to growth during the wet massing period. However, granules formed in the 27-30% liquid window were reasonably uniform in size and shape. SEM images showed that the granules did not disintegrate after dissolution but instead the soluble components were leached from the granules, leaving behind an insoluble matrix (see Fig.1).

This study shows that "steady state" granulation is a feasible approach for the production of mono-sized spherical granules. By tuning the formulation, the desired dissolution rate can be achieved to optimize the drug release rate, which opens up potential avenues in the design for paediatric granules or orally disintegrating mini-tablets.

[1] J.N. Michaels, et al., Powder Technology, 189(2) (2009) 295-303.

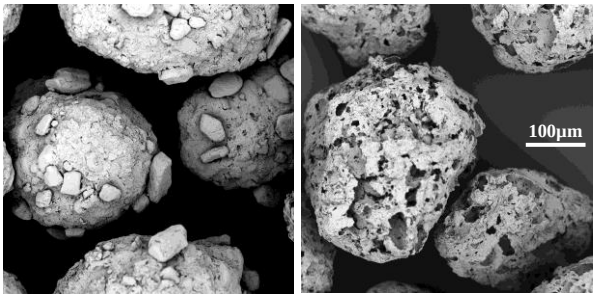

Figure 1: Structure of granules produced from "steady state" granulation at 0 minutes (Left) and 60 minutes after dissolution in water (Right).

93. PREPARATION AND INVESTIGATION OF LYSOZYME-CONTAINING PELLETS BY USING A QUALITY BY DESIGN APPROACH

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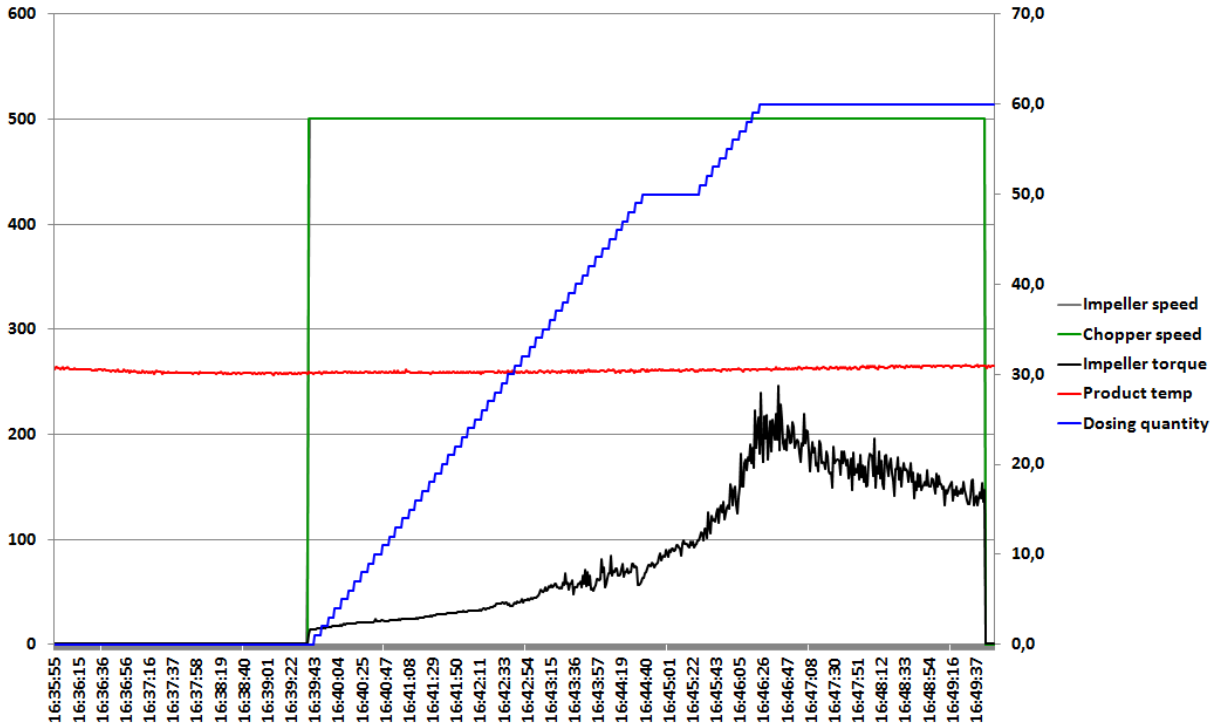
Quality by Design has increasing importance in the pharmaceutical industry, especially in the development of biotechnologically produced APIs. These proteins/peptide like materials usually shows higher sensitivity to environmental and process parameters as the small molecules.

In present work, lysozyme was used as model API, and the effect of the production parameters of an extrusion-spheronization process to the critical quality attributes (CQAs) of pellets was studied. The experiments were performed according to a 2^6 factorial design with repetitions for robustness analysis. The process parameters were recorded with PAT tools. As CQA the pellet hardness and geometry, and the activity of the API were studied. The results showed that the process parameters have considerable effect on the mechanical and geometrical properties, but less influence to API activity. Nevertheless, general activity depletion is observable directly after production, but it is reversible and recovers during storage. The cause of this phenomenon is studied with spectroscopic and thermal analytical methods.



Recorded data of the kneading process

94. CHARACTERIZATION OF GRANULAR MIXING PATTERNS IN A FLUID BED ROTOR PROCESSOR

Johannes Neuwirth[1], Sergiy Antonyuk[1], Stefan Heinrich[1] & Michael Jacob[2]

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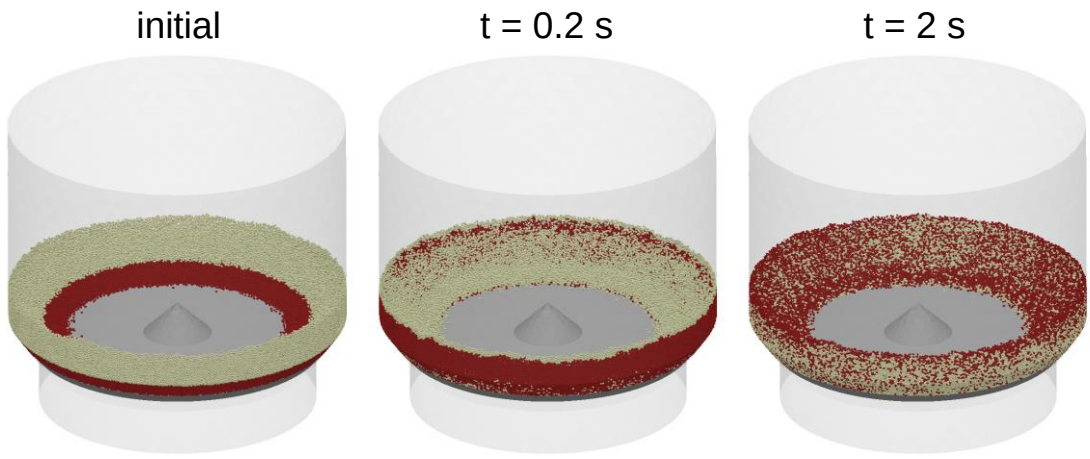
2 Glatt Ingenieurtechnik GmbH, Nordstraße 12, 99427 Weimar, Germany

In pharmaceutical, food and chemical industries the application of the fluid-bed rotor processor (FBRP) for the production of dense granules with a high strength and sphericity is widely distributed. For a better understanding of the granulation process a detailed knowledge of particle motion is essential. In general, rotor-based granulation equipment are characterised by a high mixing performance, which is an important quality parameter.

In this work the complex granular flow and the mixing patterns in a fluidized bed rotor processor are investigated. The Discrete Element Method (DEM) coupled with the computational fluid dynamics (CFD) is used to characterise the influences of the process parameters: rotorspeed and fluidization gas velocity on the particle dynamics and thus the mixing efficiency. A viscous and capillary force model was implemented to describe the interactions between surface-wetted particles. The mixing is quantified by using dispersion coefficients based on the numerical approach. In this contribution the flow and segregation of mono as well as bi disperse spherical particle blends are investigated. Finally, the mixing rates are characterized by homogeneity analysis based on the CFD-DEM simulations.

The mixing quality within the rotor processor was found to be strongly depend on the fluidization air velocity.



Time dependent mixing degree for a mono-disperse granular system.

95. A NOVEL NON-INTRUSIVE PARTICLE TRACKING MEASUREMENT TECHNIQUE FOR DENSE GRANULAR FLOWS

Johannes Neuwirth[1], Stefan Heinrich[1] & Michael Jacob[2]

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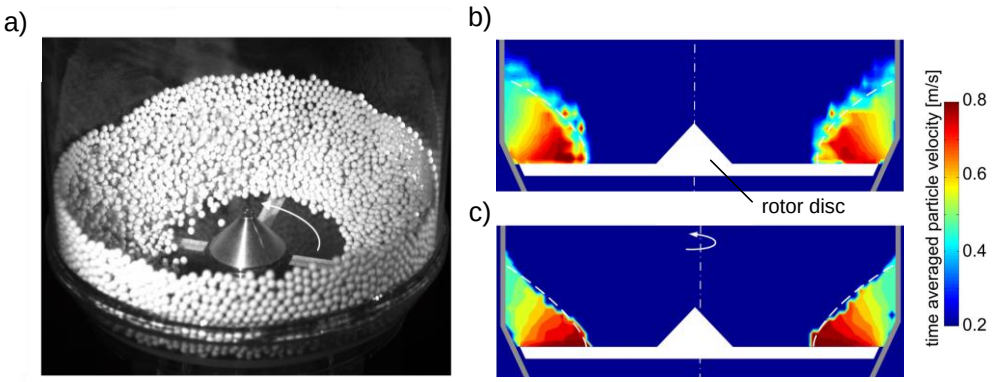
2 Glatt Ingenieurtechnik GmbH, Nordstrasse 12, 99427 Weimar, Germany

Measuring the particle motion in granular systems has been an area of increasing interest in recent years. As an example, for the understanding of the mechanisms of granulation or blending processes a detailed knowledge of the particle dynamics is essential.

To visualize and quantify the flow field and particle motion, a novel non-intrusive 3D measurement technique, the Magnetic Particle Tracking (MPT), has been further developed for granular systems [1],[2]. The MPT technique is based on the continuous analysis of a quasi-static magnetic field emitted by a single magnetic tracer particle. Due to the precisely defined magnetic dipole axis of the tracer particle, the MPT allows for the first time a detailed tracking of the translational and rotational movement of particles. Thus, the translational and rotational motion can be simultaneously measured in a dense granular flow, as well as in two-phase fluid-gas systems.

In this contribution, the MPT technique is used to evaluate the granular flow and macroscopic particle dynamics in the dense gas-solid system of a fluid bed rotor processor. The time-averaged velocity profiles and distributions, as well as residence times in several zones, e.g. spray and shear zones are determined. The information obtained by MPT can be used to optimise the design of a wide range of industrial process systems. Furthermore the MPT is an appropriate tool to validate Discrete Particle Simulations [2].



Granular flow in a fluid bed rotor processor (a), time averaged particle velocity field determined by MPT (b), time averaged particle velocity field by DEM (c).

[1] H. Richert, O. Kosch, P. Görnert: Magnetic Monitoring as a Diagnostic Method for Investigating Motility in the Human Digestive System. Magnetism in Medicine, WILEY-VCH Verlag, 2006.

[2] J. Neuwirth, S. Antonyuk, S. Heinrich, M. Jacob: CFD–DEM study and direct measurement of the granular flow in a rotor granulator, Chemical Engineering Science (in press), DOI: 10.1016/j.ces.2012.07.005.

97. ARCHITECTURE OF THE MULTISCALE SIMULATION ENVIRONMENT FOR MODELLING OF FLUIDIZED BED GRANULATION

Maksym Dosta & Stefan Heinrich

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The fluidized bed granulation process is one of the most widely used processes in the solids industry. Due to the complex thermodynamics and growth kinetics even the coarse analytical approximation of the process behaviour in most cases is an impossible task. Therefore, to analyse, to optimize it and to develop control strategies the different numerical simulation tools are used.

Nowadays, there exist various modelling approaches and software systems which are applied for the calculation of fluidized bed granulation. These systems describe the process on different time and length scales. From one hand, this can be the macroscopic scales, where the entire granulation plant can be calculated by a flowsheet simulation system. From other hand, the interactions between individual particles can be effectively modelled on the microscale by the Discrete Element Method (DEM). However, only the usage of the multiscale simulation methodology, where the submodels from different scales are combined together, allows to obtain precise estimation of the process dynamics.

In this contribution the novel simulation framework and its application to the fluidized bed spray granulation is presented. The novel system comprises the process description on four different scales. On the macroscale the flowsheet simulation system for solids processes is used. The mesoscale model is used to predict heat and mass transfer, which occurs in the apparatus and to approximate particle wetting through a nozzle. On the microscale the coupling between DEM and CFD systems is used to obtain particle dynamics in the apparatus. The submicroscale is used to calculate breakage of agglomerates.

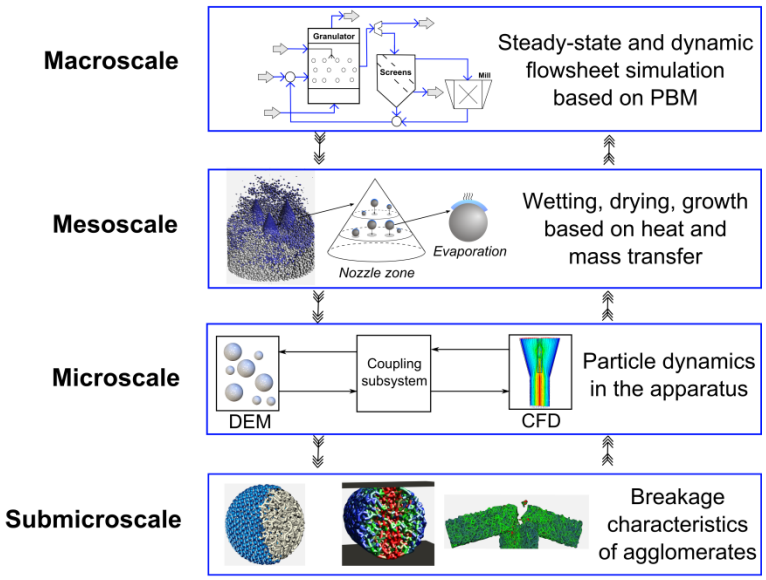

Figure 1. General representation of the system architecture.

98. INFLUENCE OF VISCOUS FORCES ON COLLISION DYNAMICS IN A FLUIDISED BED GRANULATOR: A DEM-CFD STUDY

Lennart Fries[1], Sergiy Antonyuk[2], Stefan Heinrich[2], Gerhard Niederreiter[1] & Stefan Palzer[1]

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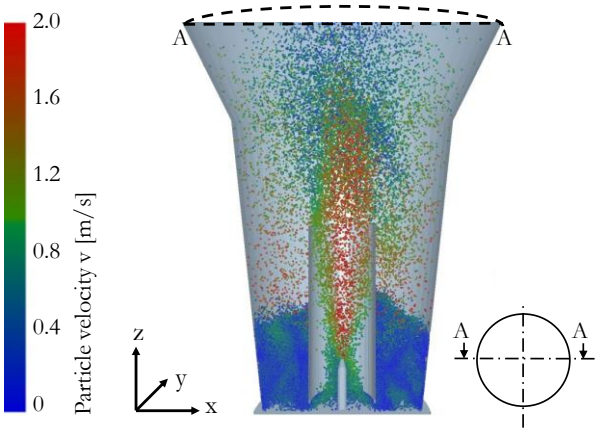
Size-enlargement and structuration processes in fluid beds such as granulation and agglomeration play an important role in the pharmaceutical and fine chemical industries as well as in food technology to improve the flowability and the instant properties of solid products. The dynamics of these processes are governed on the micro scale by a complex set of particle interactions such as wetting, particle impacts, agglomeration, sintering, drying, solidification and breakage. Profound knowledge on these mechanisms is needed to understand the influence of individual process parameters on the final product properties.

A promising approach to model particle interactions in fluidised beds is the Discrete Element Method (DEM) coupled with Computational Fluid Dynamics (CFD). In this contribution the particle and collision dynamics in a fluidised bed granulator are studied in detail for the example of a Wurster-coater, which is a bottom spray equipment with inserted draft tube. Dry particle interactions are described by a visco-elastic contact model, while a viscous force model is used to take into account particle wetting. If the entire collision energy is dissipated by viscous forces, agglomerates are formed, which can be destroyed or grow further during subsequent collisions.

Simulation results are compared to agglomeration experiments using amorphous maltodextrin in an equipment of identical geometry (Glatt® GF3 Wurster-coater). The particle size distribution of the agglomerates as a function of time and process temperature can well be correlated with the simulated collision frequency and collision velocity distribution. The strength of the produced agglomerates was characterized with a Texture Analyser. Good agreement was found between model predictions for the maximum deformation and collisional energy dissipation and experimental results in compression tests.



Simulated particle velocity distribution in a Wuster-coater.

99. AGGLOMERATION AND COATING WITH MOLTEN BINDERS

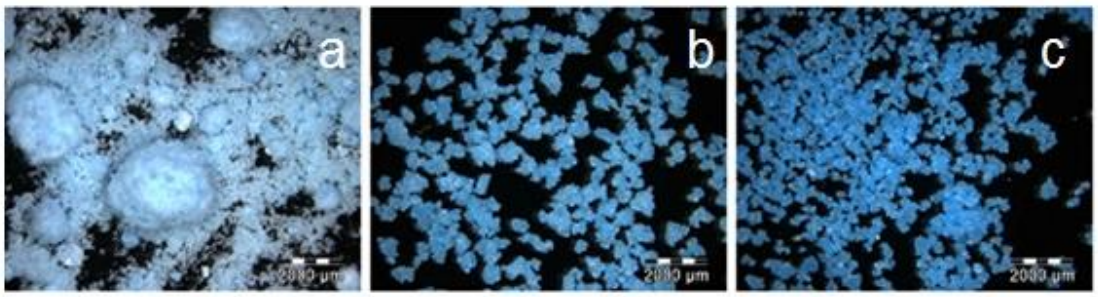
Xiana Romaní Fernández, Sven Bensmann, Robert Heinz & Frank Kleine Jäger

BASF SE Chemical and Process Engineering Research GCP/TT - L540 Ludwigshafen, Germany

Agglomeration and coating are the fundamental mechanical operations of solid particle formulation in process engineering. Water or aqueous solutions are the most commonly binders used during the agglomeration. Such binders are not suitable to be applied on high soluble solids. Furthermore, the agglomerates would then require a subsequent drying step, which can be very expensive and complex for heat sensitive materials. Thus, a better option for agglomerating heat sensitive materials is to use molten binders that build solid bridges between the particles after cooling. Depending on the operation conditions, amount of molten binder and particle system, both process agglomeration and/or coating can be performed.

In this research project, melt agglomeration was engaged in the basics of agglomeration with melts as binder, the coating with melts and the combination of both processes. Process parameters for agglomeration and coating such as binder addition technique, mixing temperature and time have been developed. The temperature influence of both melt and solid was investigated as well as the residence time and several machine parameters, such as rotation speed and mixing tool. The experiments were performed in a batch high shear mixer with intensive energy input and with a plough share mixer with low energy input. The melt was added through a heated dropping funnel or through a jet nozzle. Various molten binders and particle systems were tested.

The experiments showed that the particle size and morphology together with the wettability of the material are the main factors, which has significant influence on the result of the agglomeration process. Hydrophylic/hydrophobic behaviour plays rather a minor role in the process. Among other parameters which were investigated, such as melt dosing velocity and addition technique did not strongly influence the agglomeration, as long as the melt is sufficiently atomized. However, the difficulties related to the addition of high viscous melts which cannot be easily sprayed should be taken into account during the process design.



Three different lactose particle systems with a) fine, b) middle and c) big particle sizes treated with a blue coloured molten binder.

100. DISCRETE PARTICLE MODELING FOR TAILORED SPOUTED BED

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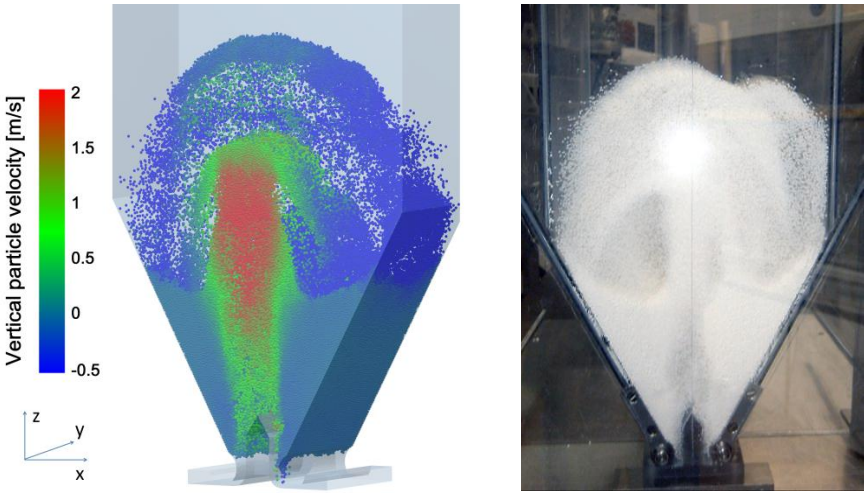
2 Department of Chemical Engineering and Chemistry, Eindhoven University of Technology, P.O. Box 513, 5600 MB Eindhoven, The Netherlands

Spouted beds are used for miscellaneous applications such as drying, agglomeration, granulation or coating and encapsulation of solids and for chemical reactions, whereby the optimization of the process demands a tailored apparatus configuration.

In this contribution Discrete Particle Model (DPM) simulations were used to gain a deeper understanding of the particle and fluid dynamics in a novel spouted bed with two horizontal adjustable gas inlets. It was found that gas flow, friction, and angle of the symmetric side walls have a pronounced influence on the mobility and the rotation of particles. Additionally, periodical fluctuations of pressure drop, indicating stability of the spouting, were also obtained from the simulations as well as from experiments. Using DPM it was possible to predict the transition from stable spouting to an instable mode by variation of gas flow rate, geometry (angle of prismatic region) as well as particle properties. The probability density function of the vertical particle velocity was found to remain constant in shape and location in the stable spouting regime and can therefore be used as a stability criterion. The spread of these curves can be used to quantify the mobility of the particles in the bed.



DPM simulation of instantaneous particle positions and velocity distribution in a novel prismatic spouted bed and qualitative comparison between simulation and experiment.

Acknowledgements: We gratefully acknowledge for the joint financial support by the Technology Foundation STW, The Netherlands and Deutsche Forschungsgemeinschaft (DFG), Germany. Project number HE 4526/5-1.

101. EFFECT OF RAW MATERIAL PROPERTIES ON THE KINETICS OF IRON ORES GRANULATION

Rafael A. Jaimes [1], Fréderic Van Loo[1], Jean-François Douce [2], Marek Schöngut [3], Maxime Evrard[4] František Štěpánek[3] & Eric Pirard[4]

1 Centre for Research in Metallurgy, Avenue du bois St. Jean/21 Liège, Belgium
2 ArcelorMittal Ironmaking, Global R&D | Maizières Process, France
3 Department of Chemical Engineering, Institute of Chemical Technology Prague, Czech Republic
4 Department of Minerals Engineering and Recycling, University of Liège, Belgium

This work had been focused on the iron ore granulation process and investigation of the influence of raw material properties (morphology and wettability of the primary particles) on its kinetics.

Nowadays processing of iron ores often requires a modification of particle size by granulation in order to improve further processability. Granulation is typically carried out in continuous drum granulators using water as a binder, and involves multiple components besides iron ore, such as return fines and other recycled materials (dusts, mill scale, sludges), solid fuel (coke breeze or anthracites) and fluxes (limestone, lime, olivine, dunite or dolomite). As it is necessary to maintain a consistent quality of the granules (size distribution, porosity, etc.), despite of the varying iron ore supplies, the question arises as to how the properties of the iron ore powder (its morphology and wettability) influence the granulation process.

A comparison of three types of iron ores (magnetite, hematite and goethite) using a laboratory-scale batch drum granulator will be presented. The wettability of the powders has been characterised by contact angle measurement; furthermore the amount of liquid absorbed into the pores as well as the amount of interparticle liquid required to promote granulation have been assessed. The results confirm the hydrophobic character of magnetite and hydrophilic character of goethite. The granulation kinetics (evolution of particle size distribution as a function of time) of each type of iron ore has been measured, and the structure of the granules (porosity, distribution of primary particles) has been characterised using x-ray tomography. Finally, the mechanical properties – namely the resistance to attrition and breakage during impact – of the produced granules have been determined.

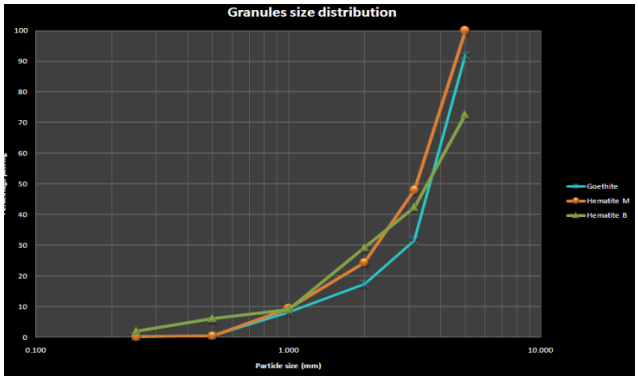


Fig.1: Example of granule size distributions

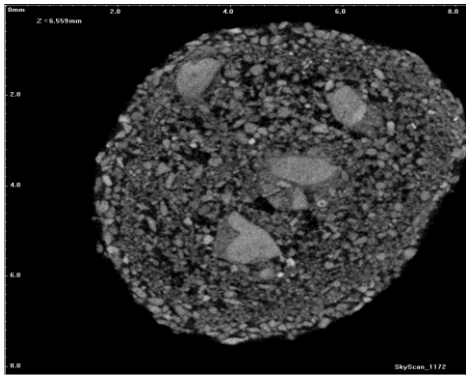


Fig.2: Microstructure of a single iron ore granule obtained by x-ray tomography

102. THE INFLUENCE OF THE PAN PELLETIZER ROTATIONAL SPEED AND THE BINDER CONCENTRATION ON THE AGGLOMERATION OF ALUMINA OXIDE GRANULES

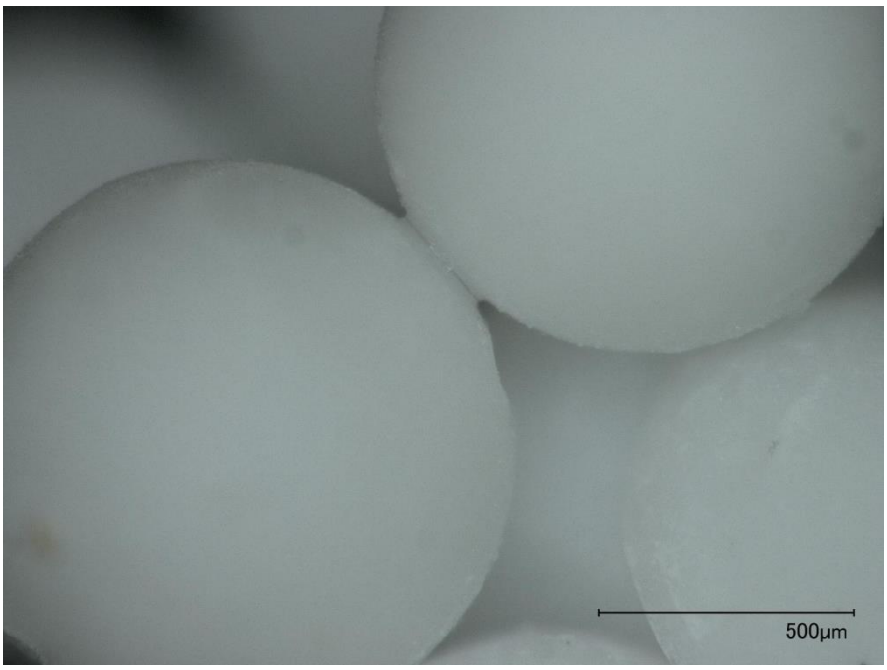
Zheni Radeva, Akif Hameed, Peter Müller & Juergen Tomas

Institute of Process Engineering, Mechanical Process Engineering, Otto von Guericke University, Magdeburg, Germany

Gaining a high agglomeration rate and better agglomerate strength is a main purpose for every agglomeration process. For optimizing the agglomeration process of industrial produced granules, using liquid binders, it is necessary to understand the mircointerations between primary particles and binder and the marcointeraction between the agglomerates themselves. In order to investigate the influence of the rotational velocity of the pan pelletizer on the agglomeration rate and the mechanical properties of the produced agglomerates, the obtained structures have to be basically analyzed.

Agglomeration of industrial produced Alumina Oxide granules is carried out in a rotating pan pelletizer. Polyvinylpyrrolidone (PVP) solutions with different concentrations of are used as binder. The rotational velocity of the pelletizer pan is previously measured and calibrated. By changing the rotational velocity of the process chamber it was found that the increment of the rotating speed leads to decrement of the agglomeration size. The high velocity leads to higher rotational kinetic energy and this causes breakages of the agglomerates. It was also proven that the high concentration of the binder solution causes a better agglomeration rate.

The conclusions from the experimental work help us to understand the basics of agglomeration process and tend to develop and facilitate the operating with particle collectives in science and industry.



Solid Matter Bridge between the particles

103. NUMERICAL AND EXPERIMENTAL STUDY OF THE MECHANICAL BEHAVIOUR OF MALTODEXTRIN AGGLOMERATES

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Fluidized bed spray agglomeration is a commonly applied process in food, fine chemicals and pharmaceutical industries to create powders with desired product properties. In this work maltodextrin is used as a model substance of an amorphous material. Primary particles are agglomerated by spraying water into a fluidized bed of maltodextrin beads (d = 2.5 mm). The wetting of the particles changes the mechanical properties of the surface and leads to the sticking and agglomeration. Depending on the agglomerator geometry and the process parameters different agglomerate structures are formed having a strong influence on the product properties, e.g. storage and handling stability or the dissolution behaviour.

As the properties of the solid bridges and the contact area between the primary particles are different for all agglomerates an experimental setup was built to create agglomerates with defined contacts. The shape was varied to compare different geometrical forms e.g. spheres or cylinders and irregularly formed agglomerates.

Experimental and numerical studies were carried out to investigate the influence of different agglomerate properties (solid bridge diameter, strength, stiffness) on the mechanical behaviour. For the simulation of the agglomerates the developed simulation environment MUSEN [1] was used to describe the particles with the Discrete-Element-Method (DEM). The agglomerates were tested in virtual (Fig.1) and real compression tests to analyse the influence and sensitivity of certain parameters on the agglomerate stability. The obtained relationships are used to improve the contact model used in the DEM code.

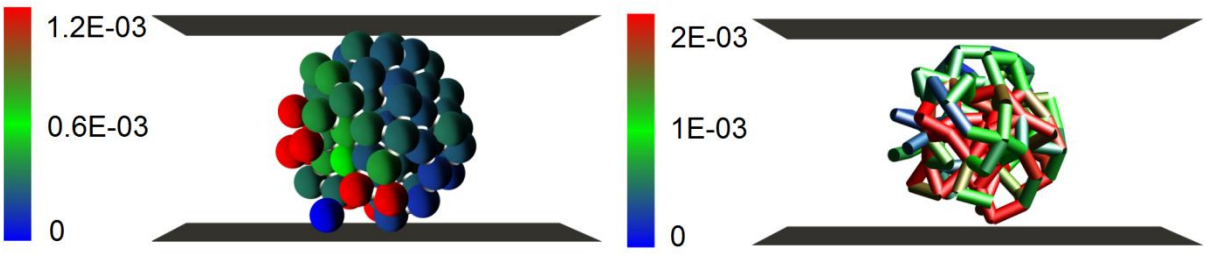

Fig. 1: Virtual compression test. Particle velocity [m/s] (left), total force in bonds [N] (right)

[1] M. Dosta, S. Antonyuk, S. Heinrich, Multiscale Simulation of the Fluidized Bed Granulation Process, Chem. Eng. Technol. 2012, 35, 1-9.

104. ENVISIONING THE FACTORY OF THE FUTURE: CASE STUDY ON CONTINUOUS GRANULATION AND TABLETTING

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It is not a surprise to hear that the pharmaceutical industry is under pressure. Many countries are cutting their health care budget resulting in reduced prices and reimbursement rates. This evolution negatively affects gross profits and sales volumes. Increased competition takes place due to generic companies aggressively seeking to extend their market share. The R&D success rate of ethical pharmaceutical companies is substantially decreasing while patent protection of block busters of the '90's is slowly but surely fading away.

All these factors lead to declining company revenues while increased R&D budgets are required to keep up R&D success rates of the past. This requires each entity of a company to drastically increase its efficiency. Product Development will need to find ways to speed up development and transfer. The Supply Chain entity as a result will need to reduce costs, improve production economics and increase manufacturing flexibility. Continuous processing technologies can play an important role in achieving these challenging objectives.

Together with a number of pharmaceutical companies, GEA Pharma Systems has been conducting studies to build a strong understanding of capabilities and constraints of ConsiGma™ technology and process. The case studies aim at proving the business value of the new technology in 4 areas: time, quality cost, and agility.

Current status of the feasibility study allows the team to confirm already some of the business values set forward in the business case. Using the ConsiGma™ technology, process development can be done in a very short time. Assuming development and commercial manufacturing is done on the ConsiGma™ 25 line, technology transfer has become redundant, resulting in a substantial time-to-market reduction. Cost of development will decrease accordingly. The agility of the system, thanks to the flexible process technology, has been proven during process development resulting in effective and efficient design of experiments. Process stability and robustness has been proven by those different long runs (between 1 and 16 hrs) during which tablets of consistent quality have been produced. Real-time, in-line measurements have shown their ability to monitor the process based on predetermined intermediate and finished product attributes and to detect minor changes in these attributes' values. They represent a promising infrastructure allowing to monitor and control the process as well as to introduce real-time-release testing.

105. EXPERIMENTAL AND NUMERICAL INVESTIGATIONS OF A SPOUT FLUIDIZED BED WITH DRAFT PLATES

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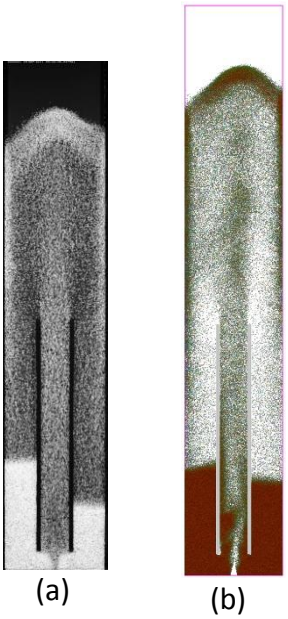
Spout fluidized beds are often utilized for gas-solid contacting operations involving physical and/or chemical transformations such as drying, coating, granulation, combustion, gasification etc. This is because these beds combine advantages of both spouted and fluidized beds. Since the development of the spout fluidized bed, several geometrical modifications have been proposed to optimize the bed performance. One of these modifications includes insertion of a draft tube inside the bed, which results in improved performance by providing a restriction on lateral particle flow. Moreover, the insertion of the draft tube leads to a stable spouting at lower flow rates, due to the reduced bypassing of the inlet gas (from spout to annulus).

In this work, the hydrodynamic characteristics of a spout fluidized bed with draft plates was studied to identify the flow characteristics by constructing a flow regime map by means of image analysis and a fast Fourier transform of the measured pressure signal. In addition, the captured images were used to determine the particle velocity via. particle image velocimetry (PIV). Furthermore, simulations were carried using a discrete particle model with a sub grid scale turbulence model. For the simulations we considered two regimes, namely the spouting-with-aeration and fluidized bed-spouting-with-aeration (dispersed spout), which are of most interest from an industrial point of view. The obtained results were compared with previously obtained experimental data i.e. PIV.



Snapshot of flow patterns obtained from (a) experimental and (b) DPM.

106. DYNAMIC IMAGE ANALYSIS OFFERS NEW APPLICATIONS IN PRODUCTION AND QUALITY CONTROL

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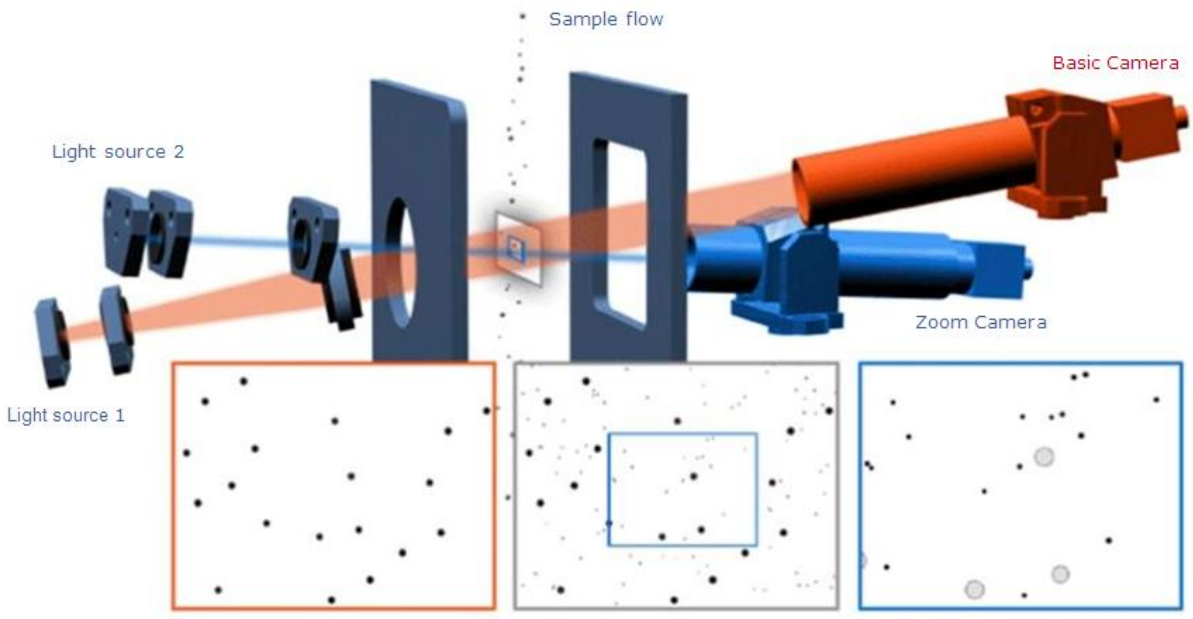
Dynamic Image Analysis has been used for the quality control of freely pourable bulk materials for more than a decade, which highlights the success and the universal suitability of this measuring method. Compared to other methods, the Dynamic Image Analysis offers crucial advantages in the measuring range from 1µm to 30mm. On the one hand, the instrumentation is easy to operate, robust and almost maintenance-free. On the other hand, the user obtains measurement results with high reproducibility and resolution in a very short time of typically 2 to 3 minutes.

Dispersed particles pass in front of two bright, pulsed LED light sources. The shadows of the particles are captured with two digital cameras. One camera is optimized to analyze the small particles with high resolution; the other camera detects the larger particles with good statistics, due to a large field of view. Each camera is illuminated by one LED with optimized brightness, pulse length and field of illumination. To cover a small measuring window of limited space with two light sources, optics and cameras, the technology was developed: the optical paths of both cameras intersect in the measurement area. Particle size and particle shape are analyzed with software which calculates the respective distribution curves in real-time.



Advanced Optical Design

108. INVESTIGATION OF DRUG RELEASE FROM TAILORED BEADS MADE OF DISSOLVED CELLULOSE

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Wet (swollen-in-water) and dry cellulose beads are used for various types of applications; immobilization, purification, separation and filtration purposes. Currently, they have become an interesting topic for pharmaceutical purposes because of their highly porous structure, which is essential for drug loading and release properties [1]. This study investigates a new coagulation-based method in producing functional particles from dissolved cellulose. The approach enables controlled tailoring of the physical (e.g. surface area, size, porosity) and chemical (interacting chemical groups) properties of the beads/particles. This in turn, allows drug loading and delivery in a controlled and a tailored manner.

In this work, cellulose beads were prepared using three different manufacturing parameters. These batches were used as drug carrier materials. Three compounds, theophylline anhydrous (Thp), riboflavin 5`-phosphate sodium phosphate (RSP) and lidocaine hydrochloride monohydrate (LiHCl). The loading procedure was carried out by immersing swollen empty beads into aqueous solutions with different API concentrations. Content analysis and in vitro drug release studies were carried out to investigate drug entrapment and release abilities of cellulose beads. Solid-state characterization of empty and loaded beads was performed using X-ray powder diffractometry (XRPD). Initial powder flow and tableting studies were also performed. The APIs were successfully incorporated inside the cellulose beads. The drug release studies showed that concentration of the loading solutions as well as preparation conditions of the beads affect the drug release from cellulose beads. In conclusion, cellulose beads from dissolved cellulose show promise as tailor-made drug vehicles in solid dosage forms.

[1] J. Trygg, P. Fardim, M. Gericke, E. Mäkilä, J. Salonen, Physicochemical design of the morphology and ultrastructure of cellulose beads, Carbohydrate polymers, (2012).

Figure 1. From the left, empty swollen beads, RSP-loaded dried beads and Thp-loaded beads compressed to tablets

109. RESIDENCE TIME MODELING OF HOT MELT EXTRUSION PROCESSES

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Pharmaceutical extrusion processes are frequently used to mix different substances, leading to homogeneous dispersion. Generally, it can be distinguished between the distributive and dispersive mixing. One of the relevant parameters characterising the extrusion process is the residence time, which was investigated by a new mathematical model evaluating a tracer concentration over time.

The extrusion process can be divided in two sub-processes the transportation and the mixing. Assuming plug flow the transportation is described by a step function (eq. 1), where c is the tracer concentration and t is the time.

$$c(t) = c_{\max} \frac{1}{2}\left[sign(t)+1\right] \qquad \text{eq. 1}$$

Considering the bolus administration of the tracer the mixing process consists of an invasive and an eliminative term having using the same rate constant (k). Based on this the Bateman function can be simplified to:

$$c(t) = c_{\max} tke^{-kt} \qquad \text{eq.2}$$

The time needs to be corrected by the dead time, which can be expressed by the dead volume (V_{dead}) and the material flow (dV).The rate constant can be expressed as the quotient of the material flow (dV) and an apparent mixing volume (V_{mix}). Coupling the transportation and the mixing term the tracer concentration over time is given by:

$$c(t) = c_{\max} \frac{1}{2}\left[sign\left(t - \frac{V_{dead}}{dV} \right) + 1 \right] \left(t - \frac{V_{dead}}{dV} \right) \frac{dV}{V_{mix}} e^{-\frac{dV}{V_{mix}}\left(t - \frac{V_{dead}}{dV} \right)} \qquad \text{eq. 3}$$

Whereas c_{max} is related to the amount of tracer applied.

In order to verify the model hot melt extrusion experiments were performed using a twin screw extruder (Mikro 27GL-28D, Leistritz, Nueremberg, Germany) using Xylitol as model compound. A tracer (theophylline) was added as bolus at time zero to the hopper of the extruder. The amount of tracer was quantified by UV spectroscopy at 292 nm (Lamda 25, Perkin Elmer, Ueberlingen, Germany). A software algorithm was used to fit the parameters of the function c_{max}, V_{dead} and V_{mix} by minimising the residuals.

The presented mathematical model, namely the Bateman function, was extended to describe the residence time distribution of hot melt extrusion processes. A good agreement between the experiments and the model was found.

111. AGGLOMERATION OF CASSAVA STARCH IN A PULSED FLUID BED

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& Florencia C. Menegalli[2]

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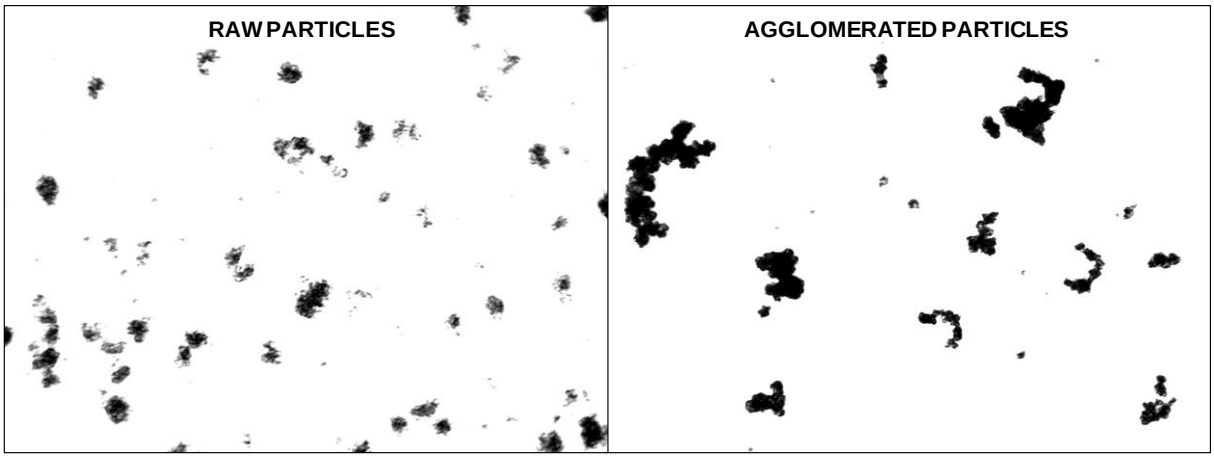
2 Laboratory of Process Engineering, School of Food Engineering, University of Campinas, UNICAMP, 13083-862, Campinas, SP, Brazil

Fluid bed agglomeration is commonly used to improve the instant properties of food powders. However, the fluidization of food ingredients is characterized by cracks and channels. Vibration or pulsation systems are frequently attached in the fluid bed equipments in order to improve the bed homogeneity and to allow the particles fluidization using lower fluidizing air flow. The aim of this work was to study the physical property modifications of cassava starch particles produced by a wet-agglomeration process in a pulse-fluid bed. The equipment used was a batch-fluidized bed equipped with a rotating spherical valve installed below the air distribution plate that promotes the fluidizing air pulsation in the frequencies of 300, 600 and 900 rpm. The process time, atomized binder flow (aqueous solution of maltodextrin, 50% w/w, at 27 °C), atomization pressure, nozzle height and mass of sample were maintained fixed at 50 min, 1.3 g/min, 0.5 bar, 300 mm and 0.40 kg, respectively. The fluidizing air temperature and velocity were fixed at 95 ºC and 0.3 m/s. The product transformations were determined by an analysis of the particle diameter, size distribution, morphology and flowability index - Flodex Tester. During agglomeration, the raw particles coalesce, resulting in the formation of granules with increasing size, but morphological changes were also verified. The Sauter mean diameter (D3.2) of the raw material and agglomerated product increased from 98.3 µm to 373.5 µm, 218.1 µm and 223.8 µm, at the pulsation frequencies of 300, 600 and 900 rpm, respectively. Meanwhile, the flowability index varied from 24 to 18, 22 and 24, resulting in the cohesiveness decreasing for granules produced at 300 and 600 rpm. The shape of the raw powder particles were circular and compact, while the agglomerated particles were elongated, wrinkled and showed tight solid bridges. The fluidization of cassava starch particles was enhanced with the pulsation system, resulting in better fluid bed homogeneity.



2D microscopic images of raw and agglomerated cassava starch particles

112. STUDY OF SOY PROTEIN ISOLATE AGGLOMERATION IN A PULSED FLUIDIZED BED USING GUM ARABIC AS BINDER AGENT

Vanessa G. Machado, Talita A.M. Hirata & Florencia C. Menegalli

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Agglomeration is a size growing process used to improve or modify end-use properties of powders. In food industry agglomeration allows producing instant products dispersing and/or dissolving quickly in liquids [1]. Fluidized bed agglomeration is one of the suitable processes leading to agglomerates with high porosity and good mechanical resistance for handling and packaging [2]. The soy protein isolate contains a high amount of protein and small fractions of fat, carbohydrates and fiber, and it is widely used as an additive in the food industry, but it is characterized as being a cohesive powder, presenting cracks and channeling formation during its fluidization [3]. The aim of this work was to select the operational conditions for producing agglomerated soy protein isolate in a pulsed fluidized bed using experimental design. Samples containing 0.15 kg of a commercial soy protein isolate were used as raw material for the agglomeration experiments. The process was carried out in a pulsed fluid bed (air pulsation frequency of 600 rpm) and aqueous solution containing gum arabic was used as liquid binder. A 2^4 complete factorial design with 3 central points was used to evaluate the influence of the variables fluidizing air temperature (65-85 °C), fluidizing air velocity (0.51-0.67 m/s), binder flow rate (0.5-2.5 ml/min) and binder concentration (5-25%) on the responses mean particle diameter, process yield and product moisture content. The results indicate that the variable binder flow rate had a more significant effect on the dependent variables studied. Surface response analysis led to the selection of optimal operational parameters, following which larger granules with low moisture content and high process yield were produced. When compared to raw material, agglomerated particles showed good handling properties, presenting wetting time decrease, free-flow improvement and cohesiveness reduction, expressing the effectiveness of the agglomeration.

References:

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[2] C. Turchiuli, Z. Eloualia, N. El Mansouri, E. Dumoulin, Fluidised bed agglomeration: Agglomerates shape and end-use properties, Powder Technology, 157 (2006) 168-175.

[3] G.C. Dacanal, F.C. Menegalli, Selection of operational parameters for the production of instant soy protein isolate by pulsed fluid bed agglomeration, Powder Technology, 203 (2010) 565-573.

113. EFFECT OF GUM AS BINDER AGENT ON CHARACTERISTICS OF PECTIN POWDER AGGLOMERATED

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The agglomeration is usually carried out at an equipment where the powder is wetted by a liquid that promotes adhesion between a particle and the other by linking bridges, leading to formation of larger particles. Gum arabic is classified as a complex arabinogalactan, containing about 2% protein and 95% about polysaccharides, obtained as sticky exudates from the stems and branches of Acacia trees. Pectin is widely used as gelling and thickening agent in the food industry. The aim of this work was to study the influence of some operational parameters in the agglomeration process of pectin and to determine the optimal process conditions which lead to a higher size increasing. The experimental runs were done according to a full factorial design 2^4 and the independent variables were: fluidizing air temperature (60-90 °C), fluidizing air velocity (0.46-0.80 m/s), binder flow rate (0.4-2.0 ml/min) and binder concentration (0-20%). Distilled water at 25 ºC with gum arabic was used as binder agent. The raw material used was pectin, high pectin methoxyl, extracted from citrus fruits, and obtained commercially. The tests were performed in a pulsed fluidized bed (air pulsation frequency of 600 rpm). As the result, particles size increased substantially and the process agglomeration produced dust-free granules with good handling properties (flowability, mechanical resistance and wettability). The pectin agglomerated avoided the formation of lumps during rehydration under gentle stirring.

114. GRANULATION OF INDOMETHACIN AND HYDROPHILIC CARRIER BY FLUIDIZED HOT MELT METHOD: THE DRUG SOLUBILITY ENHANCEMENT

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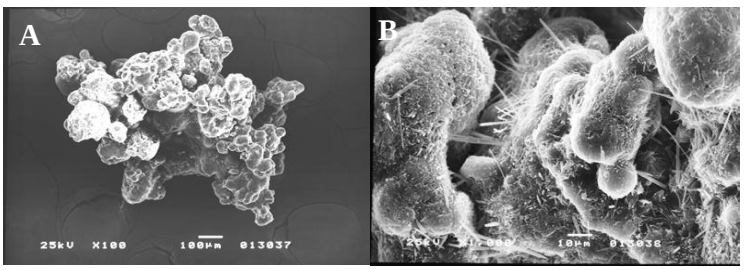
Fluidised hot melt granulation (FHMG) is a granulation technique for processing pharmaceutical powders that has gained attention as a tool to improve the solubility of poorly water soluble drugs or for sustained release formulations. Several process and formulation parameters of this technique have been shown to significantly influence pharmaceutical granulations characteristics.

The goal this work was to evaluate the effects of spray nozzle air flow rate (L/min), dispersion feed rate (mL/min) and amount of dispersion added on fluidizing carrier (g) using a three-factor, three-level Box Behnken design on the characteristics of granules of prepared by FHMG. Fifteen granulates prepared using indomethacin as model drug, polyethyleneglycol 4000 as the hydrophilic carrier and the spray dried lactose as the fluidizing substrate were tested. Dependent variables were the granulates mean particle size distribution (D_{50}) and flow properties. Furthermore, a complete characterization of the granules properties and of the drug/carrier interactions was investigated using differential scanning calorimetry (DSC), hot-stage microscopy (HSM), scanning electron microscopy (SEM), Fourier transform infrared spectroscopy (FT-IR), X-ray powder diffraction (XRPD), and *in vitro* dissolution of the drug.

The D_{50} values ranged from 479µm to 824 µm. However, response surface ANOVA showed that D_{50} was not affected by the parameters studied. ANOVA also showed that only the flow properties were affected by the factors studied significance level 5%. Low spray nozzle air flow rate values (45 to 25 L/min) produced granules with excellent flow properties. DSC and FT-IR analysis showed that there was no drug interaction during the process. The results of XRPD, HSM and SEM evidenced the presence of indomethacin crystals on the granules. The dissolution profile of indomethacin was remarkably improved. The unprocessed indomethacin released only 45% in 120 minutes whereas the granule released 100% of drug in 20 minutes in phosphate buffer media (pH 7.2). Therefore, the results confirm the high potential of the FHMG technique to obtain granules with enhanced drug solubility and release rates.



Scanning electron micrographs of granulates. (A) granulates, 500×; (B) granulates, 1,000×.

115. FLUIDIZED BED HOT MELT GRANULATION OF PIROXICAM FOR PHARMACEUTICAL PURPOSES

Marília M.S. Vieira, Rodrigo M. Martins & Luis A.P. Freitas

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The improvement of drug solubility is among the most challenging tasks in pharmaceutical development due to the high number of new active pharmaceutical ingredients (APIs) with limitations imposed by poor solubility in water. Solid dispersion is a useful method for dispersing these APIs in the molecular state in a hydrophilic polymeric carrier improving their solubility and dissolution properties. Fluidised hot melt granulation (FHMG) is a promising alternative to prepare granulated solid dispersion containing these APIs. Therefore, the aim of this study was to investigate the FHMG of Piroxicam (PRX), polyethylene glycol 6000 as the hydrophilic carrier and the spray dried lactose as the fluidizing substrate. The effects of the spray nozzle air flow rate (L/min), axial position of the spray nozzle (cm) and amount of fluidizing substrate (g) on granules properties were investigated using a Box Behnken factorial design. The dependent variables evaluated were the mean particle size distribution (D_{50}), drug content and flow properties of the granules. Furthermore, the granules were also characterized using differential scanning calorimetry (DSC), scanning electron microscopy (SEM), Fourier transform infrared spectroscopy (FT-IR), X-ray powder diffraction (XRPD), and *in vitro* dissolution of the drug.

The D_{50} values ranged from 453.5 µm to 894.7 µm and PRX content was above 83.2%. However, the response surface ANOVA showed that D_{50} and PRX content were not affected by the granulation conditions. On the other hand, ANOVA showed that the flow properties, such as Hausner factor and Car index, were usually affected at the significance level of 5%. Figure 1 shows the effects of granulation factors on the Hausner factor (HF) and Car index (CI). DSC and FT-IR analysis showed that there was no PRX interaction during the process. The results of XRPD and SEM evidenced the presence of PRX crystals on granules surface. The dissolution profile of PRX was remarkably improved. Therefore, the results confirm the high potential of the FHMG technique to obtain granules with enhanced drug solubility and release rates.

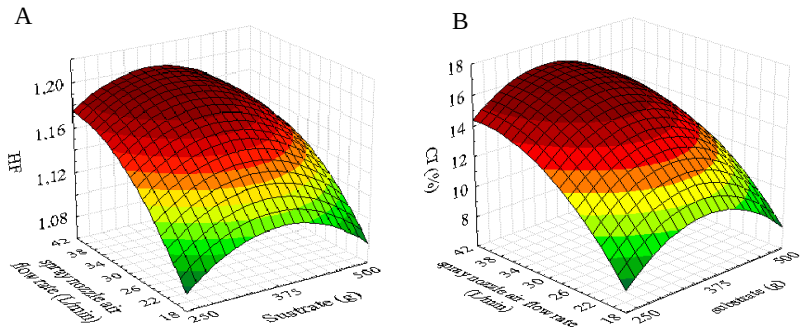

Fig. 1. Response surface for Hausner factor (A) and Car index (B) as functions of spray nozzle air flow rate (L/min) and substrate (g).

116. ONE STEP FLUIDIZED BED DRYING AND ENCAPSULATION OF A HERBAL EXTRACT

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Currently, the demand for herbal preparations has increased significantly in the food and pharmaceutical sectors, forcing the industries to develop methods for the quality control of these products in terms of quality, safety and efficacy. Dried phytochemical preparations (or dried herbal extracts) are technologically viable for large-scale production due to greater physical, chemical and microbiological stability, as well as the possibility of standardizing the bioactive compounds. Dried extracts are obtained by drying of compositions contained bioactive compounds extracted from plant materials (flowers, fruits, roots, leaves and so on). Several techniques can be used for drying extracts, being the spray drying normally used by the nutraceutical industries. In most situations, however, the spray dried powdered product present some disadvantages, such as elevated hygroscopicity and small sized and low density products; leading to inadequate flow and reconstitution properties; causing serious difficulties in post processing operations. The use of adequate drying carriers or the product agglomeration has been proposed as methods to improve physicochemical product properties, aiming to overcome these problems. On the other hand, moving beds, such as spouted and fluidized bed, have been applied in several industrial operations, including drying, agglomeration, and particle coating.

Therefore, the aim of this work is to investigate the capability of the fluidized bed process for one step drying and encapsulation of a medicinal plant extract, giving a product with high load of bioactives, and improved physical and chemical properties (e.g. particle size and flow properties). The experiments were carried out in a top-spray fluidized bed loaded with microcrystalline cellulose seed particles (MCC), of mean diameter of 150 and 300 μm. The fluidized bed is equipped with a perforated plate distributor with 110 mm of diameter, installed at the bottom of a slight conical piece, which is connected to a cylindrical column with 150 mm of diameter. A preliminary characterization of system fluid dynamics was carried out in order to determine the minimum fluidization velocity (Umf), and the gas flow ranges to be used in the drying/encapsulation tests; which were carried out with compositions based on a model plant extract. The model plant extract added with carriers (maltodextrin and Arabic gum) were atomized on to the fluidized bed of MCC particles maintained at 60 ^{o}C and fixed gas flow rate ≈ 3.0 Umf). Several operational problems, such as system collapse and irregular agglomeration, occurred in several runs, which could be linked to the operating conditions and amount and type of carrier used in the extract feed composition.

117. EFFECT OF GLASS TRANSITION TEMPERATURE ON MALTODEXTRIN AGGLOMERATE GROWTH IN FLUIDISED BED

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Particle agglomeration of a fine powder allows modifying some of its physical properties (size, shape, porosity, density) to improve its end-use properties (flowability, wettability, solubility). Fluidised bed agglomeration consists in spraying liquid (water or binder solution) on a bed of fluidised particles in order to create sticky regions on their surfaces. Agglomerate formation takes place when the sticky particles collide and form liquid or viscous bridges that are dried and consolidated by the fluidisation hot air. The repetition of these steps (spraying, wetting, collisions, adhesion, drying) allows agglomerate growth. Agglomeration of water insoluble particles needs the atomisation of a solution containing a binder to form a sticky surface that will allow bridge formation at the moment of collision between particles. However, if the particles are water soluble and contain amorphous components, water can act as a plasticizer creating a sticky region on the particle surface when it reaches the rubbery state corresponding to a critical surface viscosity [1]. In this case, particle stickiness depends on their composition and on the temperature and humidity conditions within the fluidized bed.

The aim of this work was to study the role of the glass transition temperature (Tg) on agglomerates growth and properties during fluidize bed agglomeration for two model powders (maltodextrines DE 12 and DE 21), soluble in water and with different Tg and hygroscopicity.

Experiments were performed in a bench scale batch fluidized bed granulator (UniGlatt, Glatt, Ge), top spraying water (20°C, bi-fluid nozzle) on 350 g of initial particles (180 - 200 µm) fluidized by hot air with constant hot air flow rate and temperature. Samples (1-2g) were taken along trials to measure particle size distribution and water content of the different size fractions. Final agglomerates and powders were characterized for the size, size distribution, structure, wettability and flowablity.

Due to the different properties of maltodextrine DE12 and DE21 powders, the evolution of the sample water content during agglomeration was different for both, but the evolution of the median diameter and of the particle size distribution was similar. In the studied conditions, the growth mechanism was therefore not influenced by the different values of Tg of the two powders, but this may have an influence on the structure and properties of the agglomerates obtained.

Experiments in different conditions leading to different temperature and humidity in the fluidized bed should allow going farther in this study.

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118. A "UNIT CELL" APPROACH FOR EXTRACTING MACROSCOPIC COALESCENCE AND BREAKAGE KERNELS FROM DEM SIMULATIONS

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Developing predictive models of wet granulation processes remains a challenge due to the complexity of powder flow in the granulators, as well as the complexity of the physics governing the key rate processes that control granule attributes. Multiscale models show great promise in modeling the complex granulation process. Current multiscale modeling techniques focus on utilizing compartment models with population balances (PB) [1], [2]. In these examples, Discrete Element Method (DEM) simulations are used in the multiscale framework to provide powder flow information to predict mixing patterns in the granulator and flow of powder between compartments. However, DEM can also be used to validate the macroscopic kinetic expressions for important rate processes such as coalescence and breakage. DEM can help not only determine the model parameter values, but also critically evaluate the best form of the rate process model to implement in the PB.

This paper focuses on methods to determine the rate process expressions for coalescence and breakage using information gathered from DEM models. Two simple particle flow models: (1) simple shear flow and (2) impact with a moving blade, are simulated using DEM to mimic regions in a real granulator such as a horizontal shaft, high shear granulator. Flow information and collision level data such collision frequency, velocity and energy, are used to critically evaluate different rate process expressions for coalescence and breakage. Careful consideration is given to the contact models and material properties used in the DEM as previous work has shown collision level data is a very sensitive to changes the contact model parameter values [3]. By taking this "unit cell" approach, real granule sizes can be readily simulated. A proposed experimental set up to validate the unit cell simulations is presented and discussed. Implications for the development of predictive, multiscale models are discussed.

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[2] J. Li, B. Freireich, C. Wassgren, and J. D. Litster, "A General Compartment-Based Population Balance Model for Particle Coating and Layered Granulation," *AIChE Journal*, vol. 00, no. 0, 2011.

[3] B. Freireich, J. Litster, and C. Wassgren, "Using the discrete element method to predict collision-scale behavior: A sensitivity analysis," *Chemical Engineering Science*, vol. 64, no. 15, pp. 3407–3416, Aug. 2009.

119. DRYING-INDUCED STRESSES IN PHARMACEUTICAL GRANULES PREPARED BY CONTINUOUS PROCESSING

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In pharmaceutical science and industry the strategic vision is now changing from batch processing to continuous and semi-continuous tableting production methods [1-3]. Such technique requires development and implementation of in-line real-time quality control systems, which should rely on the knowledge of the process specifics and the effect of process variables on the product quality [4]. Therefore, model-based process and product design becomes highly important [5].

There are several continuous tablet manufacturing lines in the market; one of them is ConsiGma™ (GEA Pharma Systems). This installation consists of wet high-shear granulation, fluidized bed drying, evaluation and compression units. Recently, Mortier et al. [4] applied the mechanistic model [6], originally developed for evaporation of droplet of suspension/solution, to describe the drying behaviour of a single wet granule of pharmaceutical material in a fluidized bed of ConsiGma™ setup. The calculated granule parameters were in good agreement with experimental data. This investigation testifies on behalf of high versatility and universality of the fundamental modelling approach, and feasibility of theoretical description of transport phenomena attributed to the fabrication of granules.

Our previous investigations [7] show that drying-induced thermal and mechanical stresses can appear in the granules produced for the range of temperatures and diameters offered by ConsiGma™ system. Such stresses may affect the essential properties and quality of the granules, their tableting ability and, in some cases, lead to cracking/rupture of the obtained product. In the present contribution, we describe a theoretical method to assess the magnitude of such stresses as a function of granule size and process temperature.

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[7] M. Mezhericher, A. Levy, I. Borde, Heat and Mass Transfer and Breakage of Particles in Drying Processes, Drying Technology, 27 (2009) 870-877.

120. THE EFFECT OF BINDER VISCOSITY ON THE AGGLOMERATION MECHANISMS STUDIED THROUGH THE USE OF TEXTURE ANALYSIS

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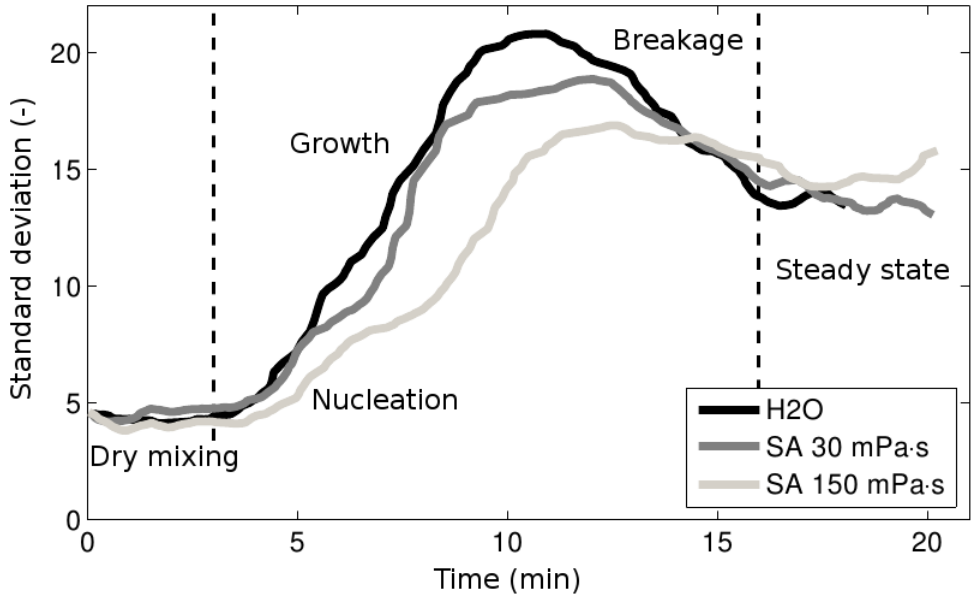
In this work agglomeration experiments have been carried out in a low shear planetary mixer and the effects of four different liquid binders (water, xanthan gum, ploy vinylpyrrolidone and sodium alginate aqueous dispersions) at six different viscosities (in the range 8-250 mPas) have been studied. In order to isolate just the effects of binder viscosity the powder formulation was taken as simple as possible (300 g of microcrystalline cellulose; T1 Ph. Eur) and the solid binders where pre-dispersed in water and not added as powder to the dry cellulose.

The evolution of the system after binder addition was followed by mean of textural analysis on images taken from the surface of the bed of powder within the mixer. It was shown that high viscosities allow the formation of final larger granules even if the nucleation and the growth are retarded. It was also shown that binder viscosity alone cannot explain difference in granule size since different binder dispersion with the same viscosity produced granule of different size. The chemical nature of the binder has to be considered in addition. An analysis of the granulation regime in the low shear mixer has also shown that experiments have been carried out in the induction growth regime and that the drop penetration time can be correlated to the agglomeration kinetics.



Example of the effects of increasing binder viscosities on the agglomeration mechanisms.

121. TEXTURAL ANALYSIS OF THE SURFACE OF A BED OF POWDER AS A TOOL TO INVESTIGATE AGGLOMERATION MECHANISMS

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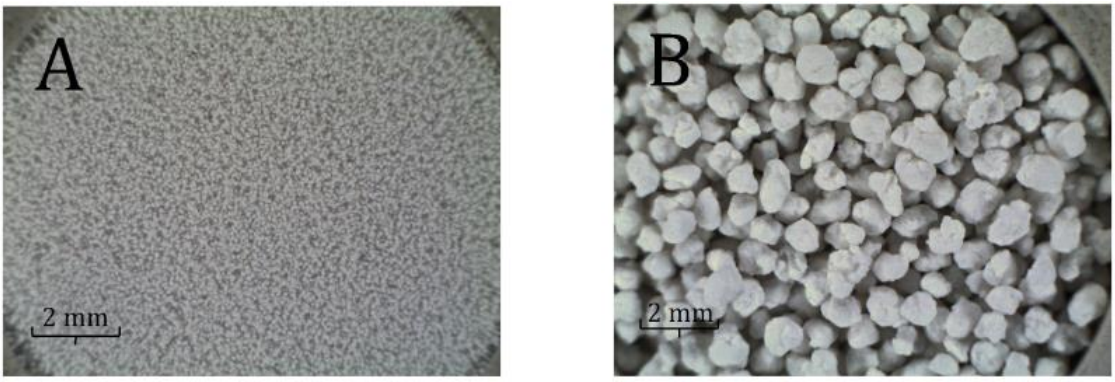
Monitoring the behaviour of a wet bed of powder and follow its evolution during time is of paramount importance in order to investigate the basic mechanisms of agglomeration.

In this work it is described the implementation and the use of a technique based on the inspection of the surface of a bed of powder in a low shear mixer after addition of the liquid binder. The technique works on digital images of the bed surface which are processed through the analysis of the texture [1]. Global measurements of the texture have been correlated to the average size of the particles in the mixer and the evolution of the bed during time has been recorded. The main advantage of the analysis of the texture surface is that the particles are not analyzed individually.

Different textural analyser have been considered. In particular, increasing the level of complexity, those based on the average value, the standard deviation, the moments of the gray level histogram, and the gray level co-occurence matrix (GLCM) analysis have been implemented and compared. On the whole 11 statistical descriptors have been used.

Provided that a sufficient portion of the bed surface can be analysed the effect of different rate phenomena such as wetting, nucleation, granule growth and breakage in the wet mass can be observed. A further potential of the method consists in the quality assessment of raw materials. To make an example unexpected small differences of particle size in the microcrystalline cellulose used in the experiments were detected and their effect on the process monitored.

[1] J. Russ. The Image Processing Handbook, 3rd Edition. Boca Raton, FL:CRC Press, 1999.



Differences of texture as a function of two different granule size.

122. GRANULATION REGIME MAP FOR BROWN COAL

Evone C. W. Tang, Emily L. Perkins, Andrew F. A. Hoadley &
Karen P. Hapgood

Department of Chemical Engineering, Monash University, Melbourne, Australia

One of the features of Victorian brown coal is its high moisture content (around 60-70 wt%) which makes drying essential before it can be transported to minimize cost of transportation [1]. However, dewatered brown coal crumbles into a fine dust and its associated large surface area and general reactivity increases its propensity to spontaneous combustion, which makes handling difficult and hazardous. Granulation of coal into coarse particles with desirable size and strength is one way to improve the handling properties of brown coal. However, brown coal is a very complex colloidal particle assembly which is soft, highly saturated, and shrinks considerably on drying. The granulation behaviour of brown coal is expected to be more complex than other better characterised initially dry materials.

In this study, run-of-mine brown coal (sourced from the Latrobe valley in Victoria) with 60 wt% as-received moisture content is granulated with water in a 0.37 m diameter laboratory drum granulator. The effect of binder content (1.4 - 4.2 wt% liquid premixed with coal in a tray before addition to the drum) and drum speed (25 - 40 rpm) on agglomeration behaviour and granule properties (e.g. size, porosity and strength) were investigated and a granulation regime map was constructed. Kerosene displacement was used to measure the granule porosity while granule strength measurements were performed by conducting uni-axial compression tests using an Instron machine. As expected, increasing the binder content and drum speed led to greater granule growth rate. Steady growth to rapid growth behaviour was observed and coal granules up to 30 mm in size were produced. Changes in granule morphology with size were observed, indicating a combination of coalescence and layering growth. The interrelationship between operating parameters (binder content and drum speed) and granule properties (porosity and strength) was studied when plotting out the regime map. The regime map developed will help to understand how brown coal granulates, to provide a better design basis and operational control of brown coal granulation processes.

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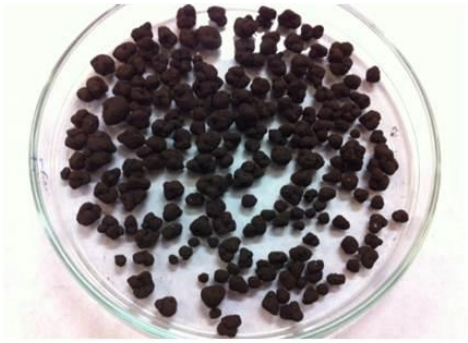

Brown coal granules from drum granulation

123. THE APPLICATION OF A MATERIALS SCIENCE-BASED APPROACH FOR DRUG PRODUCT DESIGN AND UNDERSTANDING

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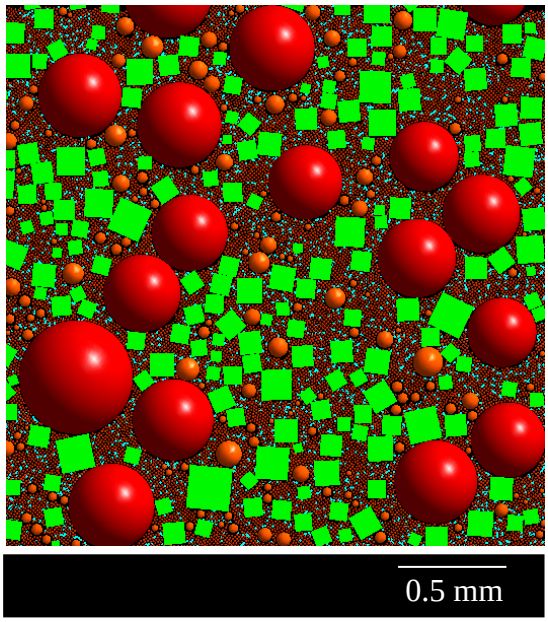
GlaxoSmithKline, Global Manufacturing & Supply, Priory Street, Ware, Herts, SG12 0DJ, UK

As the FDA has continued to adopt the principles of Quality by Design (QbD), reviews have become more question-based, and pharmaceutical companies have been required to demonstrate their understanding of their raw materials and processes at a level that is scientifically sound, feasible and justifiable. In order to effectively demonstrate such understanding, a more prominent use of physics, chemistry and engineering within a 'framework' that can guide ones efforts is required, such that the knowledge gained can be integrated effectively. It is suggested here that the discipline of Materials Science provides such a framework.

Materials Science is traditionally known as the science of metals, polymers and ceramics. It attempts to improve the performance of these 'standard' materials and also to design and fabricate new, higher performance materials that have not previously existed in nature. It is proposed in this work that the adoption of a Materials Science Approach within pharmaceutical drug development can aid with our understanding of the functionality of the input raw materials of solid oral dosage forms. It will also show how this understanding can aid in the selection of the right drug product critical quality attributes. This approach leads to more robust design space definition, and therefore enables the pharmaceutical industry to more readily demonstrate its scientific understanding of its dosage forms.



Simulation of the microstructure of an Oral Solid Dosage Form as an aid to understand the drug release mechanism

125. INVESTIGATION OF THE PARTICLE SURFACE IN FLUIDIZED BED SPRAY GRANULATION

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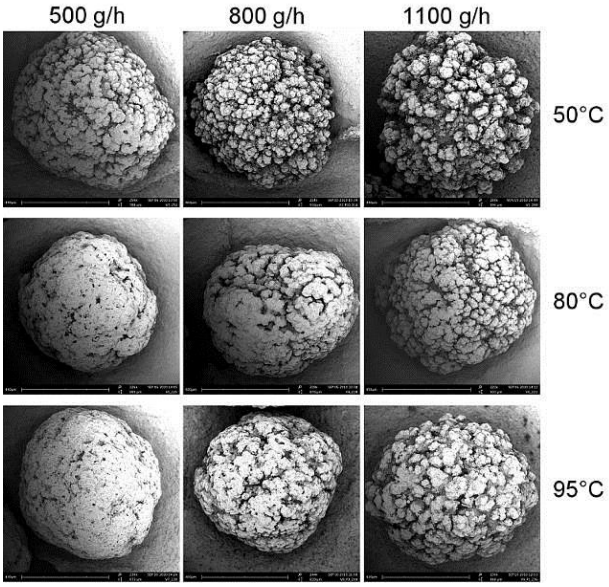
Fluidized bed spray granulation is an important process to form granular particles of a well-defined size out of e.g. suspensions, solutions, emulsions or melts. The property of the particle structure depends on the chosen process parameters. Especially in pharmaceutics and food industry specific standards were posed with respect to the granule surface. Depending on the application, the granules should dissolve rapidly or release the active ingredient over a longer period of time. These specifications require differently structured surfaces. For that purpose the influence of gas temperature and spraying rate, on the particle surface was investigated experimentally. A well-defined coating process was realized in a small lab-scale coating granulator with a top-spray nozzle. All process parameters were kept constant to run under same conditions. Only one parameter was varied in each experiment. In the first step three different temperatures were used and in the second step three different spraying rates were tested. For the experiments alumina particles were used as seeds and sodium benzoate solution as coating material. An optical analysis of the granulation products was done by scanning electron microscopy to evaluate the surface structure (SEM).

When looking at the taken SEM pictures, it can be seen that with the same primary material totally different surface structures were possible by only changing temperature or spraying rate. The reason for the formation of various surfaces with diverse porosities is the velocity of drying as a result of temperature and spraying rate, which varies from slow to fast. For example if droplets dry slower at low temperatures and high spraying rates, the formed shell is rougher and has a higher porosity. With increasing temperature and reducing spraying rate the droplets dry faster and the surface becomes smoother and more compact.



SEM pictures particle surface overview

127. LIPID MICROSPHERES MANUFACTURED BY PRILLING PROCESS: FROM RAW MATERIALS PROPERTIES TO THE FINAL PRODUCT

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Many oral drugs cause difficulties of administration and treatment efficacy due to their poor solubility in water. Lipid microspheres obtained by prilling technology provide a valuable way to enhance drug absorption and bioavailability besides other advantages from taste masking to modulated drug release.

Since several years, we have been interested in the understanding of the prilling process using lipids as binders. In line with our previous studies [1], this work involves a systematic approach which consists in determining how some critical properties of the raw material can influence each step of the process.

Prilling process consists in extruding the molten lipids through vibrating nozzles to generate calibrated liquid droplets which then rapidly solidify during their fall in a cooled air column. The size of the droplets and thus of the final microspheres was found not significantly influenced by process parameters such as extrusion pressure or nozzle vibration frequency but it was successfully modelled by Rayleigh-Weber's equation (which directly links the particle radius to some characteristics of the lipids liquid state (volumic mass, surface tension and dynamic viscosity). The rheological behaviour was shown especially crucial. With respect to the solidification step, the dependence of the lipids crystallization temperature on the cooling rate conditions appeared as the most critical parameter since supercooling phenomenon and monotropic polymorphism are often observed for these compounds. Microspheres molecular organization and structural stability were shown tightly governed by the droplet to solid prill transition step.

Critical parameters only dependent on the raw lipid materials were herein highlighted to have a significant impact on the quality of the end product obtained by prilling process. This work opens the way to further investigations which will aim, with a predictive intent, at generalizing the relationships between intrinsic lipid properties and process efficacy.

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129. OPTIMISATION OF GRANULE SIZE IN PULSED SPRAY FLUIDISED BED GRANULATION USING THE BOX-BEHNKEN EXPERIMENTAL DESIGN

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School of Pharmacy, De Montfort University, the Gateway, Leicester, LE1 9HB, UK

Top-spray fluidized bed granulation is an effective method to produce granules by spraying binder solution over the solid powder in a fluidised bed. The fluidised bed granulation is a complicated process involving multiple process variables, which have been shown to have significant influence on granulation results, subsequently on the tablet properties.

Experimental design which is one of key elements of the Quality by Design (QbD) principle has been used to study the fluidised bed granulation process. Use of experimental design allows for testing a large number of factors simultaneously and precludes the use of a huge number of independent runs when the traditional step-by-step approach is used. Systematic optimization procedures can be carried out by selecting an objective function, finding the most important or contributing factors and investigating the relationship between responses and factors. However, there is no study which has been carried out to investigate the effect of pulsed frequency on the granule properties and its interaction with other process parameters. The aim of this work was to investigate the effect of spray operating parameters including pulsed frequency, spray rate and spray atomizing pressure on granule size, granule growth rate and yield. The inter-relationship of these three spray operating parameters was also explored. Response surface methodology (RSM) is one of the popular methods in design of experiments, which involves the use of different types of experimental designs to generate polynomial mathematical relationships and mapping of the response over the experimental domain to select the optimal process parameters. Box-Behnken statistical design is one type of RSM design, which is an independent, rotatable or nearly rotatable, quadratic design having the treatment combinations at the midpoints of the edges of the process space and at the centre. A significant advantage of Box-Behnken statistical design is that it is a more cost-effective technique compared with other techniques such as central composite design, 3-level factorial design and D-optimal design, which requires fewer experimental runs and less time for optimization of a process. In this work, the Box-Behnken design was used to determine the optimal process parameters for controlling granule size with maximum granule yield and minimum span variation.

130. LIQUID MARBLES GRANULATED USING SUPER-HYDROPHOBIC METAL POWDERS

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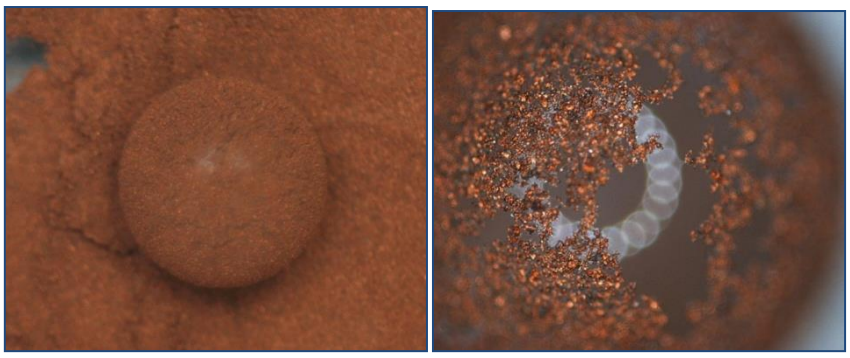
This work aims to explore the chemical engineering applications of "liquid marbles" formed using superhydrophobic metal powders, specifically investigating the use of liquid marbles as small scale reactors. The superhydrophobic powders, based on a copper substrate, were prepared by a silver deposition technique of particle sizes 9μm, 20μm and 320μm and of contact angle with water approaching 160º [1]. The liquid marbles formed using the SH copper have significant engineering advantages compared to typical liquid marbles formed by hydrophobic polymeric materials, i.e., the copper particles act as an efficient conductor of heat, allowing the temperature of the water held within the marble structure to be increased and decreased depending on the external environment. Experimental results confirm that the liquid marbles show no noticeable sign of deterioration and are mechanically robust when being held at temperatures of 70-80˚C. Due to excellent conduction properties of the copper, coupled with high mass of copper used to form the liquid marble shell (relative to the mass of water within the marble), very rapid heating and cooling of the water is achievable. Therefore, these systems offer the possibility of creating micro reactors for applications to pharmaceuticals and fine chemicals. The figure below illustrates that although the surface of the liquid sphere may be covered with SH powder, they can be designed to allow some free liquid surface for gas absorption and can also be easily injected with a liquid phase reactant. Moreover, due to the very high contact angles achieved using the SH copper powders, relatively large volume marbles can be formed. Experiments indicate that marbles of 7mm diameter, still maintain excellent sphericity and mechanical robustness.



Liquid marble formed using SH copper particles (liquid marble ~2mm in diameter) [1].

[1] P. McEleney, G.M. Walker*, I.A. Larmour and S.E.J. Bell, Liquid Marble Formation using Hydrophobic and Super-Hydrophobic Powders, Chemical Engineering Journal, 147 (2009) 373–382

132. THE APPLICATION OF POSITRON EMISSION PARTICLE TRACKING FOR ANALYSING THE MILLING OF ROLL-COMPACTED RIBBONS

Shen Yu[1], Chuan-Yu Wu[1,2], Michael Adams[1], Joseph Gargiuli[3], Thomas Leadbeater[3], Bindhu Gururajan[4], Gavin Reynolds[5], Ron Roberts[5] & David J. Parker[3]

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2 Department of Chemical and Process Engineering, University of Surrey, Guildford, GU2 7XH
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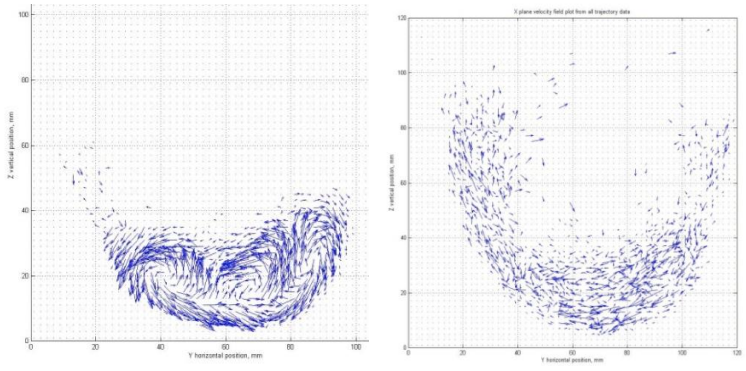
4 Formulation Science, AstraZeneca R&D, S-43183 Mölndal, Sweden
5 Pharmaceutical Development, AstraZeneca, Macclesfield, Cheshire, SK10 2NA

Roll compaction is a preferable granulation technique for powder blends that are sensitive to moisture or heat and it has been increasingly used in a number of industries, including pharmaceutical, agricultural and fine chemicals. The process involves the compaction of fine powders into ribbons or flakes that are subsequently milled to produce granules. The milling process is critical for controlling the properties of the granules, but an understanding of the governing design and operating factors is still in its infancy. Therefore, in the current study, positron emission particle tracking (PEPT) was employed to examine the kinematics of roll compacted ribbons at various milling speeds. Microcrystalline cellulose (MCC, Avicel PH-102) was used as the model feed material and PEPT measurements were performed with i) a single tracer and ii) two tracers. In the case of a single tracer, a radioactive particle (tracer) was mixed with the MCC powder and roll-compacted to form sample ribbons. They were milled using an oscillating mill at various milling speeds and quantitative information on the kinematics of the ribbons (trajectory, velocity, occupancy) were obtained using PEPT. For the two tracer measurements, one of them was embedded in a ribbon segment using the same approach as that employed for single tracer experiments, while the other was attached to the blade on the mill. The motion of both tracers were monitored simultaneously so that the motion of the ribbons relative to the blade was determined quantitatively. A close examination of the PEPT data reveals that the mill speed plays an important role: at low mill speeds, the milling process is dominated by cooperative motion of the ribbons with the blade (Fig. 1a) and the ribbons are milled primarily by abrasion; at high mill speeds, ribbons randomly move at high speeds (Fig. 1b) and ribbon milling is dominated by impact breakage.



(a) 200 RPM (b) 300 RPM

Fig.1 Velocity vector maps during milling of MCC ribbons at different mill speeds

133. CHARACTERIZATION OF PARTICLES' MOTIONS OF A GRANULAR BED IN A LOW SHEAR MIXING DEVICE

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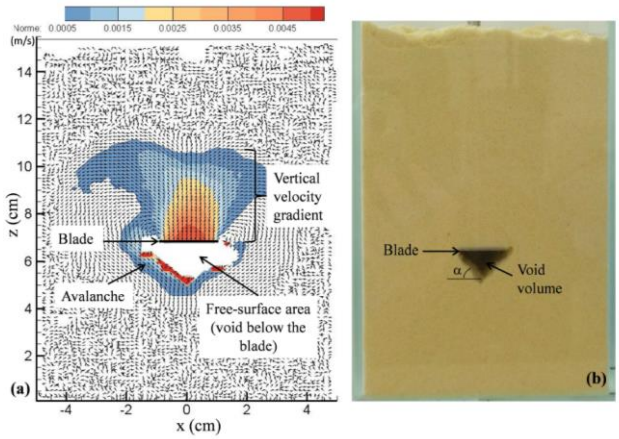
Experimental study of stress transmission and typologies of particles' motions in a powder bed under mechanical solicitations constitutes a challenging issue to achieve a monitoring of the agglomeration process, which yield is still limited to 30 or 40 % in some food processes (*i.e.* cousous process). This work relies on the visualization of the behaviour of non-hydrated grains in the neighbourhood of a blade at a controlled speed (from 2.5 to 40 $mm.s^{-1}$) in ascendant vertical motion. Force measurements at the blade scale and particle image velocimetry technique allow to identify different types of particles' motions (compaction, lateral collapsing, avalanches, *etc.*). This analysis highlights the major role of the characteristic length which refers to the static mechanical state of the granular medium. This length (analogous to the Janssen's length) is the depth starting from which the vertical stress becomes independent of depth. On both sides of this depth, two distinct rheological behaviors are identified. In the area between the surface and the characteristic length, the flow is not confined and assimilated to a free surface collisional flow. Between this length and the bottom of the cell, the granular medium is confined and the flow regime is frictional. In this area, fluctuations of stress are also identified and depend on the dimensionless blade speed. We show that these fluctuations are explained by successive loading and rupture cycles of horizontal force chains above the blade, leading to fluctuations of the vertical transmission of stress. The qualitative analysis of instantaneous velocity fields reveals the existence of a dihedral-shape assembly of grains which constitutes a permanent disturbance zone above the blade during its vertical rise whatever the blade speed and position. Finally, a specific study of the velocity gradient vertically generated above the blade is carried out for the different tested blade speeds. These results give relevant data which will help the understanding of agglomeration in a low shear mixer through the establishment of dimensionless numbers and functional diagrams. This experiment represents a rheological trial which allows to describe the behaviour of the granular bed.



(a) Instantaneous velocity fields obtained by PIV analysis when the blade is moving vertically at 5 mm/s. Velocity norm values below 0.0004 m/s are represented in white. (b) Picture of the mixing cell filled with semolina during the vertical rise of the blade.

134. IN-LINE MONITORING OF DURUM WHEAT SEMOLINA WET AGGLOMERATION BY NEAR INFRARED SPECTROSCOPY FOR TWO DIFFERENT WATER SUPPLY CONDITIONS

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The main challenge of the wet agglomeration process is to correctly disperse water in the powder bed, to ensure homogeneous water and particle size distributions and to elaborate wet agglomerates with desired properties. Different methods are commonly used to follow in-line the agglomeration process by using in situ sensors or probes, without off-lines measurements. In particular, near infra-red (NIR) spectroscopy appears as a useful non-invasive tool to extract physical and chemical information of powdered products during an on-going manufacturing process, *e.g.* in the pharmaceutical industry.

The aim of this work is to investigate the ability of NIR spectroscopy to follow in-line the agglomeration process of durum wheat semolina according to two different water supply conditions, and to describe the associated structural changes of agglomerates. A FT-NIR spectrometer is used over the whole NIR wavelength range (1000-2500 nm) with a fiber optic probe directly in contact with the powder. Raw NIR spectra as well as second derivative NIR spectra are directly analyzed. Principal component analysis (PCA) is used to qualitatively describe physical and chemical variations occurring during the wet agglomeration and to identify specific kinetics. This study reveals that analyses of spectral variations can be useful to discriminate two different processes under two different water supply conditions (*i.e.* rapid *vs* slow supply), which are associated to two different kinetic evolutions of agglomeration mechanisms inducing specific changes in size distribution and water content per size fraction. For both water supply conditions, kinetics variations of principal components (after PCA on raw and second derivative NIR spectra) are observed. NIR spectroscopy can thus be a pertinent tool to check that the on-going agglomeration process is properly done. Different characteristic times have been identified on PC scores and an attempt to link these times to changes of agglomerates physical and chemical properties have been done, mainly based on the analysis of associated loading spectra.

135. EFFECT OF IMPELLER DESIGN ON PRODUCT HOMOGENIETY IN HIGH SHEAR WET GRANULATION

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Design of small mixer impellers is not tailored for granulation as they are designed for a wide range of processes. The Kenwood KM070 was employed as a standard apparatus to undertake this investigation. Five different impeller designs were used, possessing different shapes and surface areas. The aim of this research was to evaluate the performances of these impellers to provide guidance on the selection and design for the purposes of granulation. Lactose granules were produced using wet granulation with water as the binder. The efficacy of respective granulates was measured by adding an optically sensitive tracer. This was used to determine powder concentrations within various regions of the granulator. It was found that impeller design influenced the homogeneity of the granules; and therefore can affect final product performance.

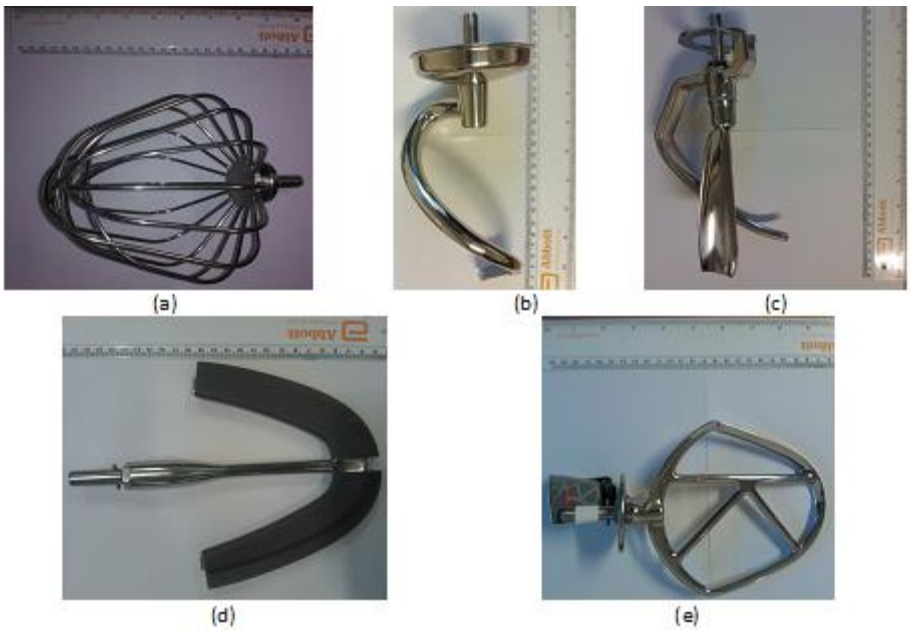

Figure 1: Various impellor designs employed.

136. EFFECT OF POWDER COMPOSTITION ON THE GRANULATION OF BINARY MIXTURES

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In most granulation processes involving processing of a mixture of powders, the powders have comparable densities and similar particle size distributions. Granulation of powders with large variation in powder densities is usually avoided due problems such as particle segregation. The granular product being designed in this work required the use of two different powders namely limestone and teawaste; these materials have different bulk and particle densities. The overall aim of the project was to obtain a granular product in the size range 2 to 4mm. The two powders were granulated in different proportions using carboxymethyl cellose (CMC) as the binder. The effect of amount of binder added, relative composition of the powder, and type of tea wasted on the product yield was studied. The results show that the optimum product yield was a function of both relative powder composition and the amount of binder used; increasing the composition of teawaste in the powder increased the amount of binder required for successful granulation. Increasing the mass fraction of teawaste in the powder mix must be accompanied by an increase in the amount of binder to achieve the desired product yield. It was found that attrition losses decreased with increasing binder content.

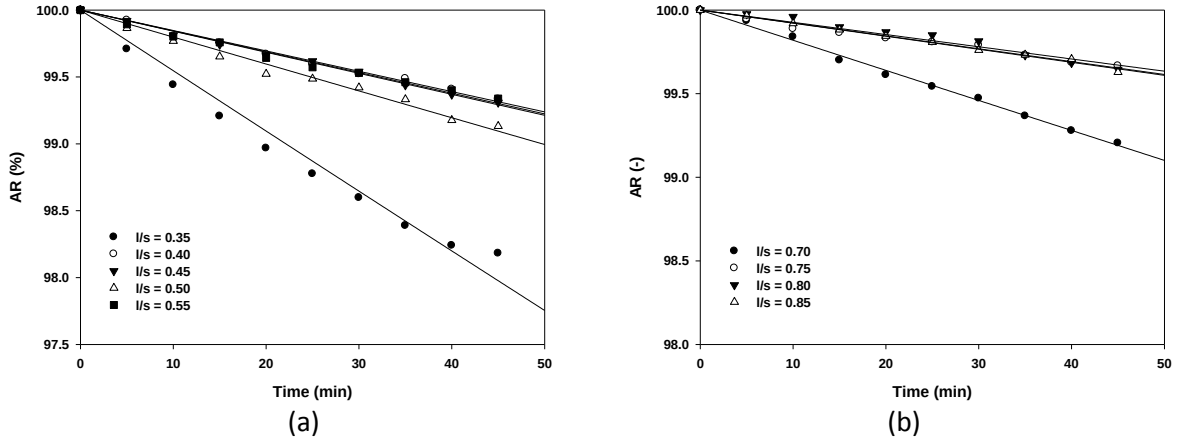

Figure 2: Effect of relative composition of the powders on attrition strength (a) Mass fraction of teawaste 0.25 (b) Mass fraction of teawaste 0.5

137. FOAM AS A NEW BINDER FOR POWDER GRANULATION: RHEOLOGY APPROACH, GRANULES PROPERTIES AND EFFECT OF GELLING PRODUCTS

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Wet granulation is a process commonly used to produce granules from individual particles. It can have different goals, for instance to maintain the homogeneity of powder mixtures, to improve flowability and compressibility properties or to control size distribution. However, all these properties are strongly depending on the process parameters, the properties of the binder and how the binder is added to the mixture.

Since the last ten years [1], a new way is explored to produce granules where the binder, before to be added, is converted to a dense foam. This method can provide many advantages like a better distribution of the binder into the powder bed, a reduction of the needed binder quantity and a reduction of the drying time and cost. Effects of formulation and process conditions on granule size distributions have ever been studied [2].

To characterize the granulation process, the torque of the main blade of the granulator device is recorded during the addition of the binder to the powder. With this rheological approach, the torque can be plotted as a function of the liquid/solid (L/S) ratio and process parameters [3].

The first step of this study is to explore the granulation of lactose-MCC mixtures in a high shear mixer, using the liquid and foam ways. In both cases, the torque measurements indicate that the granulation process could be described by the classic profile of wet granulation described with three distinct stages: wetting, nucleation and growth. Nevertheless, rheological profiles using liquid or foam ways show differences at different liquid/solid ratio which are correlated to the granule properties.

The second step is to study the granulation of highly hydrophilic powders of the family of cellulosic derivatives (HPC, HPMC). The behavior of these gelling products does not obey to the classical rheological profiles of wet granulation. Moreover, the expected benefits of the foam granulation compared to the liquid granulation are not so convincing with these products.

Keywords: foam granulation, Torque measurement, granules properties,

[1] P. Sheskey, and C.M. Keary, Preliminary report of the discovery of a new pharmaceutical granulation process using foamed aqueous binder, Drug devevlopment and industrial pharmacy, 30 (2004) 831-845.

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[3] T.M. Chitu, D. Oulahna and M. Hemati, Rheology, granule growth and granule strength: Application to the wet granulation of lactose-MCC mixtures, Powder Technology, 208 (2011) 441-453.

139. DEVELOPMENT OF A GROWTH REGIME MAP FOR A NOVEL REVERSE-PHASE WET GRANULATION PROCESS

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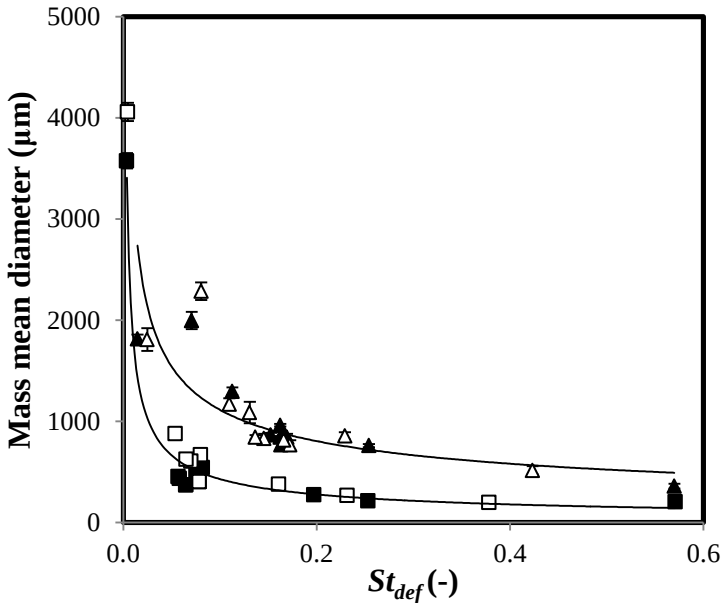
Conventional wet granulation is affected by the conditions of liquid addition, including droplet size, addition rate and powder flux through the spray zone. Subsequently, poor binder distribution, localised over-wetting and un-controlled granule growth are common challenges. To address this problem a novel reverse-phase granulation process has been developed where powder is added to liquid binder, with mixing, to form granules. This process eliminates the complex controls associated with granule nucleation and binder distribution and instead approaches the granulation process via a controlled breakage mechanism.

In the present work a growth regime map was constructed for a novel reverse-phase granulation process. A wide range of Stokes deformation numbers and liquid saturation were studied for both the conventional and reverse-phase processes by varying liquid volume and viscosity and impeller speed. Granules of hydroxyapatite and poly (vinyl pyrrolidone) were prepared using a Diosna P1-6 granulator. Significant differences were observed between the granulation processes; in particular in-process powder surface velocity, dry granule mass mean diameter, dry granule intragranular porosity and dry granule breaking strength. Stokes deformation number and liquid saturation were shown to be good process descriptors for granule mass mean diameter and intragranular porosity. The resulting growth regime map effectively described the regimes experienced under the various granulation conditions for both the conventional and reverse-phase granulation processes.



Mass mean diameter as a function of Stokes deformation number, St_{def}. ■ 10 % w/w PVP by conventional granulation, □ 20 % w/w PVP by conventional granulation, ▲ 10 % w/w PVP by reverse-phase granulation, Δ 20 % w/w PVP by reverse-phase granulation.

140. IMPROVEMENT OF ENALAPRIL MALEATE CHEMICAL STABILITY BY HIGH SHEAR MELTING GRANULATION

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Enalapril maleate (EM) is an anti-hypertensive drug unstable when it is mixed with commonly used tablet excipients. EM degrades to form enalaprilate by hydrolysis and to form diketopiperazine (DKP) by dehydration [1]. Enalapril sodium salt is widely use in the solid dosage form production due to its better thermal stability. However, there is a release of CO_2 during the reaction used for salt preparation, which is the responsible for a packaging swelling of this product [2]. Hydrophobic excipients may also improve EM stability by prevent the occurrence of hydrolytic reactions. In the present work, granules were prepared by melting granulation using stearic acid (SA) or glyceryl monostearate (GMS) as hydrophobic binders, aiming to develop more stable EM solid dosage forms. The granules were prepared in a laboratory scale high shear mixer (Diosna P/VAC 10-60, Germany). EM (5%), lactose, crospovidone and SA (10 or 18% w/w) or GMS (15% w/w) were mixed in the high-shear; then the mixture was heated up until proper granulation was achieved. The resulting granules were cooled at room temperature, mixed with extragranular crospovidone (2%) and compressed in a rotary machine. Size distribution, flow properties and water content of the granules were evaluated. *In vitro* drug release and EM chemical stability were also evaluated and compared with data obtained from EM or enalapril sodium salt tablets prepared by conventional wet granulation process performed without hydrophobic binders. Granules obtained from all formulations showed good physical properties. EM release was higher than 80% in the first 30 minutes for all tablets evaluated. The highest improvement in the EM stability was observed in formulations containing SA followed by GMS formulations. The decrease in the hydrolytic conversion to enalaprilate was the responsible to the increase in the EM stability, since DKP formation was not significantly modified. This study showed that hot melting granulation could be successfully used to prepare EM granules containing hydrophobic binders. The granules showed good physical properties, immediate drug release and better drug stability than the conventional wet granules. It isimportant to note that EM-SA tablets showed better drug stability compared to enalapril sodium salt conventional tablets and can be used as an alternative for the industrial production of enalapril solid dosage forms.

[1] M. M. Al-Omari, M. K. Abdelah, A. A. Badwan, A.M.Y. Jaber, Effect of drug matrix on the stability of enalapril maleate in tablet formulations, Journal of Pharmaceutical and Biomedical Analysis, 25 (2003) 893-902.

[2] R. L.O. Rezende, M. I. R. M. Santoro, J. R. Matos, Stability and compatibility study on enalapril maleate using thermoanalytical techniques, Journal of Thermal Analysis and Calorimetry, 93 (2008), 881-886.

141. QUANTIFY THE INFLUENCE OF INTERPARTICLE COHESIVE FORCE ON FLUIDIZATION

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In fluidization granulation process, the presence of binder forms liquid bridge between particles, which results in interparticle cohesive force. It is known that the cohesive force can change fluidization behaviour significantly. By increasing the cohesive force generally causes a transition in fluidization from Geldart B/D particle through Geldart A, to C, and finally failure in fluidization. However, it is difficult to estimate the influence quantificationally.

A number of studies aimed to characterize effects of interparticle force added viscous liquid into fluidized beds. One disadvantage is that the control of uniform liquid distribution throughout the bed is difficult. Also, it is impossible to track the variation of liquid bridge shape during fluidization which is essential for calculation of interparticle cohesive force.

In this paper, the cohesive force is controlled by coating particles with polymer whose viscosity increases with temperature. First, the polymer suspension consisting of a solution of a PEA/PMMA copolymer with 2:1 ratio was employed to coat sugar particles with a mean diameter of 1.0 mm in a rotary drum granulator (Figure 1(a)). Secondly, the coated particles were fluidized in a 2D fluidized bed. The temperature in fluidized bed can be controlled by heaters of the fluidization gas and bed vessel (Figure 1(c)).The fluidization dynamic was recorded by a CCD camera, and pressure fluctuation was measured by fast-response pressure sensors. The effect of interparticle cohesive force on fluidization is analysed in detail, and more importantly, the ratio of the interparticle cohesive force over drag force is investigated to obtain a quantitative picture of the influence of interparticle cohesive force on fluidization.

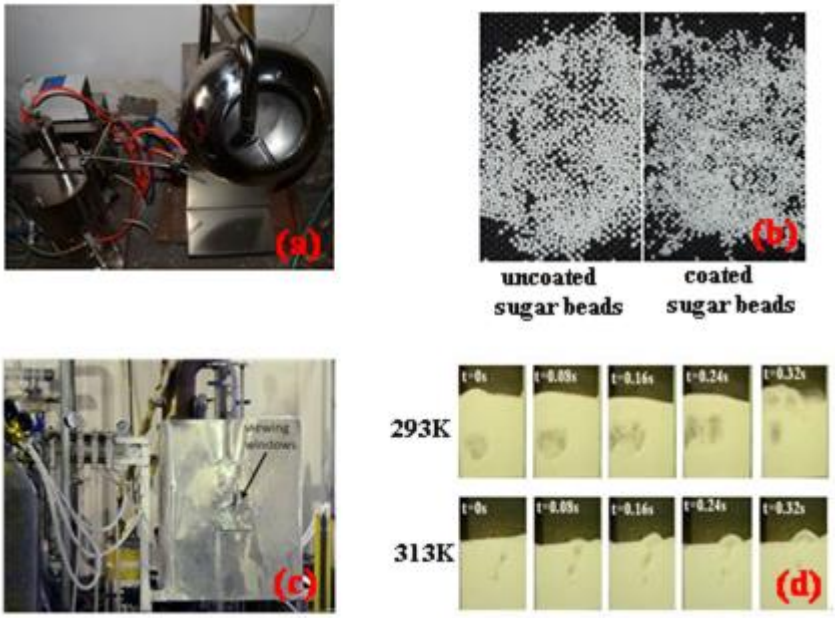

Figure 1. (a) Rotary drum granulator; (b) Image of sugar beads; (c) 2D fluidized bed; (d) Fluidization of coated particles at different temperatures.

142. BUILD-UP OF POWDERS IN AUGER FILLERS

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Build-up is the transformations of a powder to a smeared deposit adhered to a surface and is effectively a form of granulation as it involves the transformation of a number of particles into a single discreet and solid mass. Currently much progress has been made in developing understanding of situations in which powders undergo well defined changes involving the whole or a large portion of the bulk. For example the conditions under which a powder will flow out of a hopper have been investigated in great depth. However phenomena such as build-up where a small fraction of the bulk undergoes changes over longer periods of time e.g. several minutes or hours, have attracted much less attention, even though they could be the critical factors that dominate the reliable operation of a powder handling process.

Auger fillers (Fig. 1) have been used for the packing of powders in the detergent, food and pharmaceutical industries for many years. As a powder passes through the auger a number of particles are transferred through the clearance between the auger and the straight funnel, as the auger rotates. The stresses exerted on the particle within the clearance have a large effect on the powders behaviour, which depends upon the magnitude of the clearance. Crutchley & Bridgwater (1997) showed that the level of attrition experienced by particles with in a small clearance is dependent upon the ratio of the magnitude of the clearance to the particle diameter. A key finding for their study was that once the clearance exceeds 2.2 particle diameters no further attrition was observed.

Twelve surfactant containing powders manufactured by Procter & Gamble were studied. Each of these powders were placed into the hopper of an auger filler (a semi automatic filler fitted with free flow auger tooling, manufactured by ALLFILL International Ltd.). The powders were then filled with the auger rotating at 840rpm through 3 revolutions per dose, with a 1 second interval between doses. Experimental results revealed that torque increases as build-up increases and the build-up tendency decreases as the clearance is increased (Fig.2). Also it was also found that the mechanical properties of the powders studied play a role in determining whether a powder will form build-up. A key find of this work has been that for powders to form build-up they must not only contain particles capable of entering the auger/straight funnel clearance but must also have particles which are both weak and highly ductile. The twelve powders studied were characterised via uniaxial compaction with subsequent application of the Kawakita lumped parameter model and via measurements of tablet strength. It was found that powders which formed build-up had both low 1/b Kawakita parameters and low tablet strengths (Fig.3).

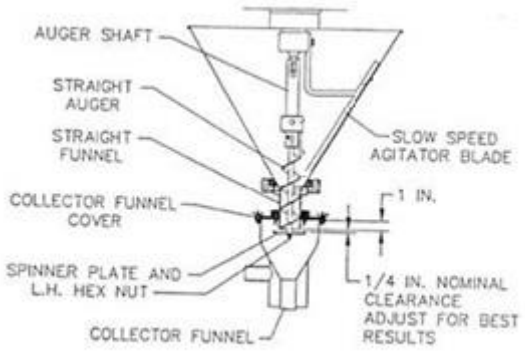

Figure 1: Schematic of an auger filler.

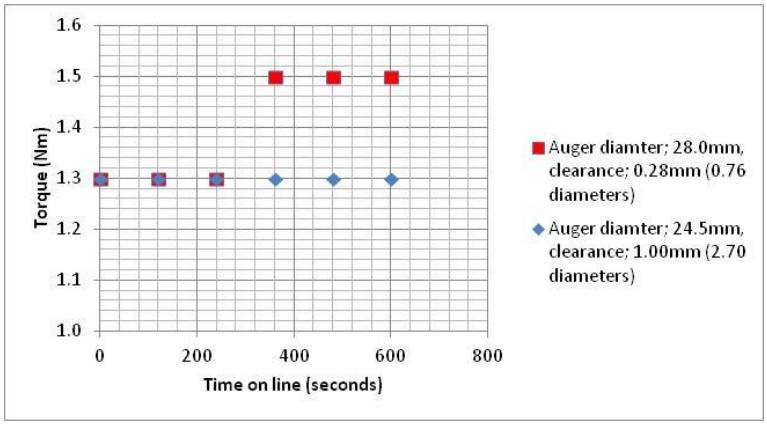

Figure 2: The effects of clearance on powder build-up.

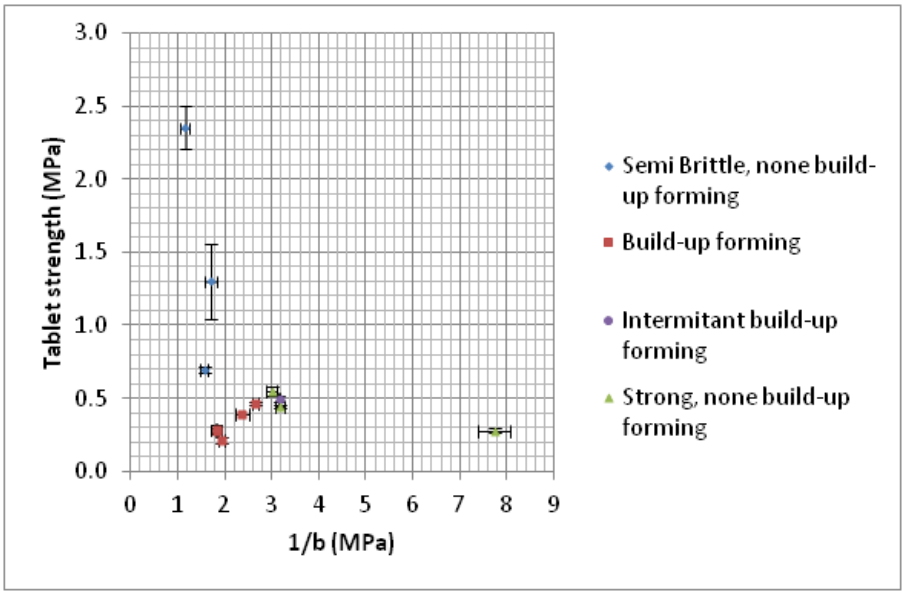

Figure 3: The effect powder properties on build-up in an auger filler.

143. CHARACTERIZATION OF THE COMPRESSION PROPERTIES OF COMPACTED CHITOSAN AS A FUNCTION OF MOLECULAR WEIGHT

Iyad S. Rashid[1], Tareq Aljallad[1], Khouloud A. Alkhamis[2], Hanan A. Hassan[1], Tala H. Altalafha[1] & Adnan A. Badwan[1]

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2 Department of Pharmaceutical Technology, Faculty of Pharmacy, Jordan University of Science and Technology, Irbid, 22110, Jordan

Investigation of the compression behavior of a compacted hydrophilic polymer of different molecular weights has been addressed herein with respect to plastic, elastic, and frictional behavior. A wide molecular weight range of chitosan, 13-250 kDa, was chosen as the model hydrophilic polymer for compaction using a roll compactor. The compacted powders were subjected to compression analysis using the Gamlen Tablet Press (GTP). Force displacement curves, Heckel/Kawakita analysis, and tablet ejection profiles were used as the methodological approaches in quantifying the plasticity, elasticity, and frictional nature of the powders. GTP results on the work for compression and elastic recovery, plasticity factor, yield pressure, degree of powder rearrangement and densification, and energy for tablet ejection have all justified the compression dependency of the hydrophilic polymer on its molecular weight.

144. INVESTIGATION OF THE EFFECT OF Mg SILICATE ADDITION ON THE POWDER PHYSICAL PROPERTIES OF COMPACTED METFORMIN-HCl

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This work has been conducted on the active pharmaceutical ingredients (API) powders which do not exhibit an improvement in their physical properties (e.g. bulk density, tap density, flowability) upon compaction. Metformin-HCl was found to illustrate such a drawback. It was suggested to investigate the effect of the addition of synthetic amorphous magnesium (Mg) silicate has on the physical properties of the compacted binary (API-Mg silicate) mixture. It was found that Mg silicate in the API-Mg silicate complex is advantageous since it was able to increase the bulk and tap densities of the compacted mixture. In addition, there was an improvement in the powder flow properties as indicated by the Carr's index and Hausner's ratio of the compacted powder. The results thereby validate the functionality of synthetic amorphous magnesium silicate.

145. THE DEVELOPMENT OF A CONTROLLED RELEASE PREPARATION COMPRISING METRONIDAZOLE AND COMPACTED HYDROPHILIC BINARY POLYMER MATRIX OF CHITOSAN AND XANTHAN GUM

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A formulation of Metronidazole controlled release tablets was developed based on the drug mixed with a hydrophilic binary polymer matrix composed of Chitosan and Xanthan gum. A roll compactor was used to attain good compressible, flowable and highly compactable powder characteristics. A universal controlled-release composition comprising a pharmacologically inactive matrix of Chitosan and Xanthan gum was tested for its ability to control the release of Metronidazole as a drug model. The effect of changing the drug: excipient ratio on the drug release profile of the Metronidazole: Xanthan Gum/Chitosan tablet was determined. A drug to polymer ratio was set constant at 1:3 by weight. The ratio of Chitosan to Xanthan gum was also varied; a 2:1 Chitosan: Xanthan Gum ratio was found to be most suitable.

146. EVALUATION OF COMPACTED PREPARATIONS COMPRISING BINARY MIXTURES OF STARCH AND MAGNESIUM SILICATE WITH MODEL LOW STRENGTH WATER SOLUBLE DRUGS

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2 The Jordanian Pharmaceutical Manufacturing Co. (PLC), Naor, Jordan

The application of a compacted binary mixture of maize starch and synthetic amorphous magnesium silicate on preparations comprising drugs of low strength has been investigated herein using a roll compactor. Bisoprolol fumarate and terbutaline sulphate were chosen as the two model drugs. Mixtures were tested for surface morphology, particle size distribution, specific surface area, and powder flowability based upon multiple compaction of the binary mixtures. Furthermore, preparations were evaluated for drug adsorption, compatibility with drugs using FTIR and DSC analysis. Results indicated improvement in powder physical properties with respect to powder flow and bulk density. Multiple compaction enhanced further powder densification along with a decrease in the powder specific surface area. The chemically inactive excipient with the model drugs, as illustrated by FTIR and DSC studies, showed no indication of drug adsorption for the temperature range 25-50 °C.

148. FAST DISSOLVING FILLERS IN DRY FOAM FORMULATION

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Dry foam technology was developed to overcome insufficient oral bioavailability of poorly soluble and wettable active pharmaceutical ingredients (APIs) [1]. In recent studies the type of filler showed to have a distinct influence on dry foam morphology as well as dissolution characteristics. It was concluded that fast dissolving low molecular weight fillers like isomalt could improve the initial dissolution of the tested dry foam formulation tablets [2]. This hypothesis was confirmed by comparing dry foam morphology and dissolution behaviour of two different soluble APIs (indomethacin, orlistat) in three different filler combinations, namely maltodextrin 21D (M21D), isomalt (ISM) and 1:1 mixture of mannitol and maltodextrin 21D (50%MTL). In addition the dissolution behaviour of dry foam tablets was compared to fluid bed granule formulations (FBGs) with the same drug loading.

For dry foam preparation API, an aqueous surfactant solution and the filler were mixed in a kneading device, resulting in a paste. Due to reduced pressure foaming and pore development occurred. Complete drying of the foam was achieved at moderately accelerated temperatures. Afterwards, the dry foam (DF) was dry sieved to obtain granules, which were after blending with an external phase further downstream processed to tablets. Dissolution behaviour was analysed in FaSSIF using USP 2 paddle apparatus and HPLC analysis after filtration.

DFs prepared with low molecular weight fillers (ISM, 50%MTL) revealed more compact and less porous morphology compared to DF M21D (Figure 1). Interestingly, their rough surface still resulted in increased surface area compared to FBG and DF M21D. The initial dissolution behaviour of indomethacin and orlistat DF tablets was improved by ISM and 50%MTL. Whereas, all indomethacin formulations reached complete dissolution of the applied dose, the total amount of dissolved orlistat was increased compared to the FBG tablets by using low molecular weight fillers in dry foam formulation.

[1] P. Busson, M. Schroeder US 7,074,431 B2 7/2006; EP 1 296 656 B1 8/2006

[2] E. Lenz, A. Sprunk, P. Kleinebudde, S. Page, The influence of fillers on dry foam properties, Partec International Congress on Particle Technology Nuremberg 2013

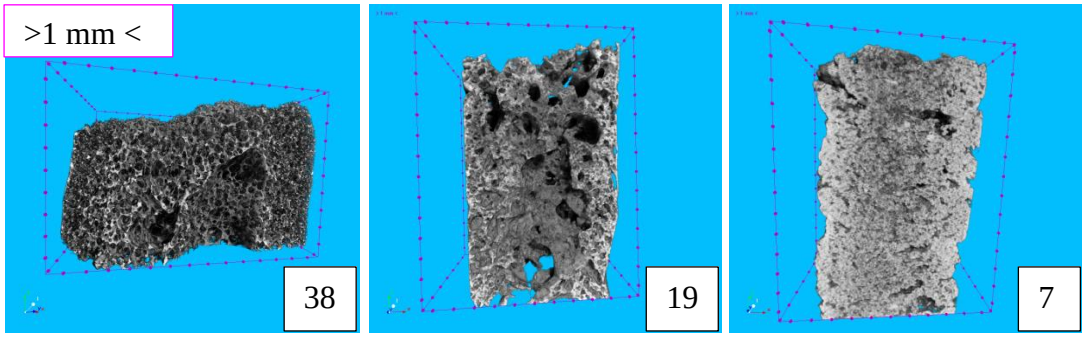

Figure 1: X-Ray microtomography images of indomethacin dry foams with corresponding expansion ratio (V_{DF}/V_{paste}) using M21D (right), ISM (middle) and 50%MTL (left) as filler

149. CONTINUOUS MELT GRANULATION: INFLUENCE OF PROCESS AND FORMULATION PARAMETERS ON GRANULE ATTRIBUTES

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The aim of this study was to screen the influence of process and formulation parameters upon the granule properties produced via a continuous melt granulation process, hence contributing to increase continuous melt granulation process understanding. Therefore, two different model formulations, i.e. an immediate release based on Polyethylene glycol (PEG), 4000, α-lactose-monohydrate and metoprolol tartrate (MPT)) and a sustained release formulation based on stearic acid and MPT, were used.

In both formulations the binders acted differently. During melt granulation of the sustained release formulation, the lipophilic binder stearic acid formed a matrix in which the model drug MPT was dispersed. During melt granulation of the immediate release formulation, the hydrophilic binder PEG 4000 acted as an agglomeration fluid by which the coalescence of the accompanying α-lactose monohydrate and MPT particles occurred. Continuous granulation was done using a co-rotating intermeshing twin screw granulator.

For each model formulation, a similar statistical screening design was created to study the effects of the following factors upon the processability and the granule properties: screw speed, throughput, temperature (increasing or stable), temperature last zone, temperature second last zone, screw design (1 or 2 mixing zones). For the sustained release formulation, also the effects of the ratio stearic acid/MPT (85/15-99/1) and the stearic acid raw material form (flakes or milled) were included in the applied fractional factorial design. For the immediate release formulation, a D-optimal design was used in which also the PEG, lactose and MPT fractions were included as factors. The design responses included several process (torque and temperature increase in barrel) and granule properties (flowability, friability, particle size distribution, homogeneity, porosity, solid state, dissolution time).

The results showed that the quality of the granules can be optimized by adjusting specific process and formulation variables. As well the process variables temperature, screw speed, and throughput as the formulation variables amount and type of binder, had a significant influence on the particle size distribution and the flowability of the melt granules; while increasing the amount of kneading blocks resulted in denser and stronger granules.

150. ONE DIMENSIONAL MODEL FOR THE PREDICTION OF RESIDENCE TIME DISTRIBUTION GRANULATION IN A TWIN-SCREW GRANULATOR

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Twin-screw granulation is considered as a promising continuous alternative for traditional batch wet granulation processes. It allows a large volume production from different formulations with a short residence time. The twin-screw granulator (TSG) is composed of both transport and kneading element modules. The extent of different rate processes such as wetting, growth and breakage involved in granulation is greatly governed by the residence time distribution within each module where individual rate processes dominate over others. Currently, visual observations and experimental data are used to determine the residence time distributions (RTD). In this study, a dynamic transport model was developed based on classical chemical engineering methods. The simulation data and the experimental residence times are compared based on the solid feed rate, the screw rotation speed and the variation in type of screw modules. The result allows validating the transport model and predicting RTD which can be later coupled with a population balance model in order to predict more realistic granulation yields in a TSG.

152. CRITICAL ASSESSMENT OF THE UNIFIED COMPACTION CURVE MODEL

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A large number of models were developed to describe the tableting process and to predict tablet characteristics. As dry granules exhibits lower compactability compared to raw material, it is particularly interesting to describe the work hardening phenomenon and the tableting behaviour of dry granules. Farber et al. [1] proposed a unified compaction curve (UCC) for uncompacted material and dry granules of plastically deforming material. As strength is generated irreversibly, the compactability curve of tablets from dry granules is shifted from the direct compression curve by the value of applied pressure during roll compaction and tensile strength of the ribbons. Using these values an exponential model could be derived to describe tensile strength of produced tablets. The aim of the study was to assess the UCC model in more detail.

Microcrystalline cellulose and magnesium carbonate were roll compacted with specific compaction forces of 2, 4, 8, 10 and 12 kN/cm. The ribbons were directly dry granulated and sieved to obtain four defined particle fractions for every batch. Granule fractions for each batch as well as the raw material were lubricated with magnesium stearate proportionally to the specific external surface area and subsequently tableted. Flat faced 8 mm tablets of 200 mg mass were produced on a rotary die press with compression pressures between 60 and 418 MPa. Tablets and ribbons were characterized.

In accordance to Farber et al. [1] the UCC model is not applicable for magnesium carbonate, as it is a brittle behaving material. Magnesium carbonate revealed a nearly linear relationship between tensile strength and compression pressure not fitting the exponential model equation.

The unified compaction curve model is applicable for MCC dry granules compacted at lower compaction forces. In accordance Farber et al. [1] the experimental data fit well the exponential model curve for compression pressures ≥ 200 MPa. For lower compression pressures data deviated from the model as described before. However, compaction behaviour of dry granules compacted at higher specific compaction forces was not well described with the model. The unified compaction curve was generated applying the tensile strength of the ribbons and the applied pressure during roll compaction. For dry granules compacted at 2, 4 and 8 kN/cm corresponding unified compaction curves were found. However, for specific compaction forces ≥10 kN/cm, especially for 12 kN/cm, the compaction curves deviated from the unified compaction curve. Solid fraction of tablets prepared at the same compaction pressure is comparable for all different dry granules. Thus, the deviation of compaction curves for higher compacted dry granules from the model could not be explained by differences in tablet density. XμCT measurements of granule tablets showed a different microstructure for granules produced at various compaction forces. Granule structure is preserved after tableting only for higher compaction forces, which could explain differences in strength.

[1] L. Farber, K.P. Hapgood, J.N. Michaels, X.-Y. Fu, R. Meyer, M.-A. Johnson, F. Li, Unified compaction curve model for tensile strength of tablets made by roller compaction and direct compression, International Journal of Pharmaceutics, 346 (2008) 17-24.

153. DESIGNING FIX-BED REACTOR FOR ESTERIFICATION USING ION-EXCHANGE RESIN AS CATALYST

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Fixed bed reactor was designed in-house from simple equipments available in laboratory. The catalyst used for designing this reactor was ion exchange catalyst and the reactor performance was verified by carrying out an esterification reaction. The spherical ion-exchange catalyst was not converted into pellets but was directly loaded. When the reactor was loaded only with catalyst the flow of reactants through the catalyst bed was found to be negligible. The flow rate was increased by adding fillers like glass beads with the catalyst particle. The reaction considered for checking the reactor performance of fixed bed reactor was esterification of lauric acid and lauryl alcohol. Since esterification of lauric acid and lauryl alcohol in batch reactor and fix-bed reactor can be correlated, designing of fix-bed reactor is proved to be successful. The activity of catalyst in this reactor was observed to be stable for 40 hrs. The advantage of this fix-bed reactor with ion-exchange as catalyst is that it can be regenerated easily.

155. EFFECT OF TYPE OF LACTOSE AND MICROCRYSTALLINE CELLULOSE COMBINATION ON RECOMPACTION

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Dry granulation and roller compaction are preferred over wet granulation for tablet production because of improved product flow properties, better content uniformity, avoidance of solvents during production and the scalability of the process. The use of microcrystalline cellulose (MCC) in these processes has the disadvantage, that the first compaction step reduces the tabletability. Lactose can be a suitable excipient when the appropriate grade is selected. Therefore, the main aim of this project was to study the effect of different grades of lactose, in combination with MCC, on tableting properties. Initial screening was done using individual grades and then the optimized grade of lactose in combination with MCC was selected and evaluated further.

In the first part of the study, three different grades of lactose i.e. Pharmatose® 125M (sieved α-lactose monohydrate), SuperTab® 21AN (anhydrous β-lactose), SuperTab® 11SD (spray-dried lactose) along with Pharmacel® 102 (MCC) were obtained from DFE Pharma, Germany. Sample blends of lactose an MCC were densified by compaction to relative densities of 0.6, 0.7, 0.8 and 0.9 and subsequently milled. The resulting granules as well as the uncompacted powder mixtures were lubricated with 0.5% magnesium stearate for 5 min. The lubricated mixtures were tableted using 20 mm punches at porosities of 5%, 10%, 15% and 20%. In the second part of the study, the concentration of MCC was optimized with the selected lactose grade, using above densification and tableting procedures.

The first part of the study showed that Pharmatose® 125M (crystalline α-lactose monohydrate) forms weak tablets, both from the powder and from the densified granules. SuperTab® 11SD (spray dried lactose) forms strong tablets when tableted as supplied, however tabletability after densification is substantially reduced. Tablets compressed with anhydrous β lactose showed formation of strong tablets and is preferred form of lactose for dry granulation led to little loss of tabletability after densification. MCC formed strong tablets as well, although it showed the well-known behaviour of reduction in tabletability. The highly recompactable anhydrous lactose was used in the second part of the study to determine the optimum lactose/MCC ratio. The undensified powder mixtures show, as expected, an increase in tabletability with increasing MCC, however this is not the case for the granules. The tabletability of the granules remains more or less constant for tablets made at higher porosities of 20% and 15%. However, for tablets made at low target porosity of 10% and 5%, tabletability decreases when the MCC proportion rises above about 35% to 45%. The optimal ratio of anhydrous lactose and MCC was found to be 65:35 to about 55:45.

156. ADSORPTION OF NANOPARTICLES ON SUGARS USING FLUID BED DRYING

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Fluid bed drying (FBD) is efficient method for granulation and can be easily scaled up at industrial level. Very limited data is available on conversion of nanoparticles to solid dry powders using FBD. Lyophilization is preferred method for conversion to dry powder, but has biggest disadvantage of high cost. The aim of this work was to adsorb nanoparticles without affecting its particle size on adsorbent like lactose and mannitol. The main challenge was to maintain particle size after drying, as the processes involve transfer of heat and mass between air and the particles which might cause some degree of stickiness depending upon the type of composition. Nanoparticles prepared by high pressure homogenization were used as granulating fluid. The aqueous dispersion of nanoparticles was sprayed in top spray assembly to adsorbent bed of lactose or maltodextrose in stainless steel chamber of FBD. The fluidization velocity and spray speed was optimized. Nanoparticles (72 nm) were successfully converted to dry powder using FBD. Off-white granules collected were spherical in nature, having particle size in range of 1 to 2 µm. The granules were dispersed in water and sonicated. The obtained supernatant filtered through 0.2 µm filter showed particle size in range of 70 to 100 nm. Lactose showed better adsorption of nanoparticles compared to maltodextrose, but the final product was slightly sticky in nature. Maltodextrose resulted in completely dry granules. The tablets compressed for both excipients were uniform in shape, no tabletting problems were faced. The tablets were directly compressed without addition of any ancillary excipients. The disintegration time was 13 and 17 minutes for maltodextrose and lactose tablet. The controlled drug release was observed for both excipients compared to marketed tablet. Thus, FBD can be employed for conversion of nanoparticles to dry powder; however detailed study for selection of adsorbent excipients must be undertaken before optimization of drying process.

Acknowledgement:

DFE Pharma, Germany is acknowledged for providing gift sample of lactose and travel support to first author.

159. AGGLOMERATION OF WET GRANULAR MATERIAL DURING DENSE FLOW

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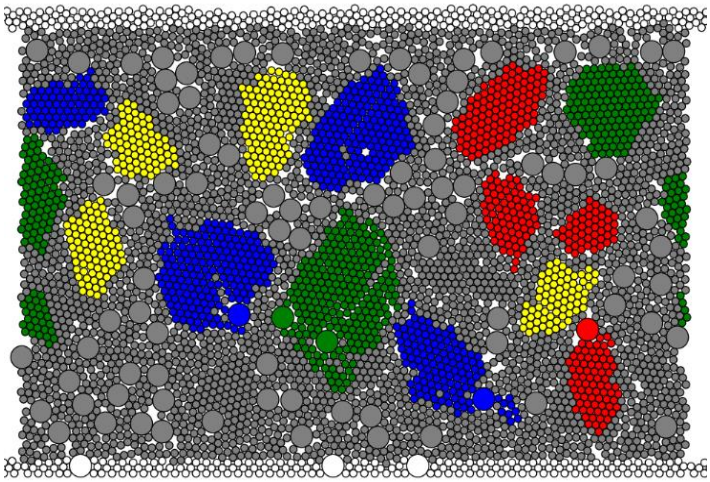
A better understanding of wet agglomeration process is of major importance in various industrial domains such as in iron ore granulation. In this work, we use contact dynamics simulation to modelize the agglomeration process during dense granular flows. We focus on the effect of capillarity forces acting at the contact point and particle granulometry. Packings of bi-disperse discs are submitted to a simple homogeneous shear flows and analyzed in the steady state. We show that a detailed analysis of the rheology described by dimensionless parameter such as the "well known" inertial number and the cohesive number allow us to describe the evolution of aggregates in terms of their sizes and lifetime.



Aggregates in a homogeneous shear flow.

160. FLOWSHEET MODELING OF AGGLOMERATION SYSTEMS: BENEFITS AND CHALLENGES, AN INDUSTRIAL PERSPECTIVE

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In recent years flowsheet models of particulate processes have become more accessible to the industrial community, and judging by the very well established use of liquid/gas flowsheet modelling, particulate flowsheet models have great potential for broad continuing application. This paper examines their application to an industrial, high shear based, agglomeration system and through a number of case studies highlights their benefits to plant optimization, scale-up and particulate product design. These case studies will also be used to highlight some of the challenges there are in practically applying these models to agglomeration plants and particulate product plants in general, and to show where industry would benefit from improvements in the state of the art of the models of these systems unit operations.

161. DRUG FORM KINETICS AS A FUNCTION OF HIGH SHEAR WET GRANULATION CAPTURED USING ON-LINE RAMAN SPECTROSCOPY

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High shear wet granulation (HSWG) is a process which transforms a poorly flowing, low bulk density drug into a workable granule using a liquid binder. Controlling HSWG can become particularly problematic when the formulation is complex for example in high drug loading, extended release formulations. These often comprise a highly soluble (*aq*) drug and excipient which can act as an additional solid binder when hydrated. During water addition a reaction between the solvent (binder) and active ingredient or excipient takes place often involving drug solubilisation, phase changes and re-crystallisation. These form changes are a risk to the defined final drug product in terms of chemical stability and bioavailability and thus are of critical importance to monitor [1].

We have used on-line Raman spectroscopy [2] to investigate the drug form change during high shear wet granulation of a high drug load, highly soluble drug formulation. The drug (in a polymeric cellulose blend) was granulated with the addition of 30% water at a controlled/ jacketed temperature of 25°C. We have investigated the effect of water content, local over wetting (spray vs. pour water addition), scale (1 vs 4L), water addition rate, wet massing time and drying method. Throughout all our experiments we observe complex changes of the drug form during granulation, manifest as reactions between the initial desolvated drug (A), hydrated form (B) and amorphous cellulose/ drug complex (C). In addition, we have investigated the effect of extended periods of wet massing (0, 60 and 600s), wet incubation time (36 hrs) and drying conditions (tray, vacuum oven and fluid bed drying) on the drug form kinetics. Interestingly we observe no change in the reactions kinetics or proportion of drug form for short wet massing times however the longer time of 600s significantly alters the reaction kinetics and final drug product form. The incubation study reveals a time of 36 hrs for reaction completion. During the slower drying techniques of tray and vacuum oven, changes in drug form continued for several hours. In contrast fluid bed drying appeared to lock the final proportions of drug form product attained during granulation, with comparatively small changes observed during drying. The final drug composition (A or B) is strongly dependent on granulation and drying conditions, whereas the amorphous form, once generated, plateaus to a consistent value for each batch. This is a key finding as controlling final drug form helps to minimise its potential risk to product performance e.g. drug product chemical stability and/ or bioavailability.

[1] International Conference on Harmonisation, Specifications: Test Procedures and Acceptance Criteria for New Drug Products: Chemical Substances, ICH Q6A, 1999.

[2] C. J. Strachan, T. Rades, K. C. Gordon, J. Rantanen, Raman spectroscopy for quantitative analysis of pharmaceutical solids, J Pharm Pharmacol. 59(2) (2007) 179-92.

162. COMPARISON OF TWO DIFFERENT FIBER OPTIC PROBES FOR THE IN-LINE NIR BASED GRANULE MOISTURE ASSESSMENT IN THE DRYING UNIT OF A CONTINUOUS PHARMACEUTICAL TABLETTING PROCESS

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Nowadays, there exists the intention within the pharmaceutical industry to move from traditional batch processing to continuous processing. Continuous production offers many advantages such as flexible batch size, reduced batch variability and no time-consuming and expensive scale up issues. It is obvious that the current conventional quality control systems of production processes, based on off-line analyses in analytical laboratories, would annul the advantages of continuous processing, and that continuous real-time quality control is indispensable for continuous production. The desire within the pharmaceutical industry to shift towards continuous processing strengthens the desire and need to invest in process analysis methods.

This study focuses on the thorough validation of an in-line NIR based moisture quantification method in the fluid bed dryer of a continuous from-powder-to-tablet granulation line (ConsiGma™-25, GEA Pharma Systems nv, Wommelgem, Belgium). The moisture assessment ability of two different fiber optic probes coupled to two different NIR spectrometers was compared: a Fourier-Transform diffuse reflectance NIR spectrometer (Thermo Fischer Scientific, Zellik, Belgium, Nicolet Antaris II near-IR analyzer) equipped with a conventional probe and an FT-NIR spectrometer (Matrix™-F Duplex, Bruker Optics Ltd, UK) equipped with a fiber-optic Lighthouse Probe™ (LHP, GEA Pharma Systems nv, Wommelgem, Belgium).

Two moisture quantification PLS calibration models, one for each probe, were developed. Twenty calibration experiments were conducted, spectra were taken at-line and regressed versus the corresponding residual moisture values obtained via Karl Fischer measurement. The most suitable PLS models for this calibration data were determined by evaluating the fit and predictive properties (i.e., via cross-validation) of the models. In a second step, the two developed NIR moisture quantification models were validated by calculating the accuracy profiles on the basis of the analysis results of validation experiments. Spectra were taken both in-line and at-line. Herewith, the within day, between day and operator variability were taken into account. Furthermore, based on the data of the accuracy profile, the measurement uncertainties for both probes were determined.

From the accuracy profiles developed for both probes, it was concluded that at the end of the drying process 95 out of 100 future in-line moisture assessments will be included within the acceptance limits (5%). The acceptance limit is the maximum accepted difference between the predicted residual moisture and the 'unknown' true residual moisture. The β-expectation tolerance interval, expressing the proportion of expected future measurements that will fall inside the acceptance limits, and the measurement uncertainty were slightly better for the LHP based moisture assessment method.

163. USING DEM AS A TOOL FOR THE DEVELOPMENT OF POPULATION BALANCE KERNELS

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Wet Granulation is a process of particle size enlargement, and is an essential operation in many industries, including pharmaceuticals, foods, minerals processing, fertiliser production, and detergents. Despite the seeming simplicity of this process, the science behind granulation is complicated and poorly understood, and as a result granulation is notoriously difficult process to predict. This has led to a lack of reliable design or scale up rules for wet granulation, and the design and scale up of granulation processes is often an expensive and time consuming exercise.

Population Balance Modelling (PBM) has the potential to be used as a tool in granulation design; however the development of PBM rate descriptors (kernels) which are flexible across different operation conditions and formulations has proven difficult. Most kernels rely on the use of fitted parameters, which vary with granulation conditions.

In this work, Discrete Element Method (DEM) simulations of a radial section of a high shear granulator have been performed, with the aim of studying the dynamic granulation behaviour. Of particular interest is the collision frequency, or the rate at which particles collide. These results will be used in the development of new population balance kernels for high shear granulation.

165. NOVEL APPROACH FOR INTERPRETING POWDER FLOW BEHAVIOUR USING POWDER ADHESION AND COHESION PLOTS

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Understanding the flow properties of particulate materials is important for the design and control of particulate processes, especially for powder storage and handling. Powder characterisation and knowledge of powder flow properties are essential to develop a good understanding of the flow behaviour of materials. The important flow properties are the inter-particle friction, wall friction, flow function and bulk density. The Ring Shear Tester can be used to determine the flow properties of powders, blends and granules, which can help in formulation development and also in process evaluation. Shear cell results can distinguish good and bad flowing samples, classify the pharmaceutical formulation in terms of its flow characteristics, be used in design of mass flow hoppers and predict friction driven process performance, especially dry granulation by roller compaction. The major difference between the shear cell technique compared to other flow assessment methods is the consideration of both powder and process equipment to interpret the flow behaviour. The shear cell results take into account the influence of process equipment on the powder flow pattern

This article describes work which has been carried out using the Schulze Ring Shear Tester to characterise Active Pharmaceutical Ingredients (API's), standard excipients, powder blends and granules, to understand the impact of cohesive and adhesive properties on the processing attributes of these materials. The data generated has been used to characterise the flow properties of the pharmaceutical granules in the form of powder and wall friction plots. This approach can be used to help mitigate flow problems during the early formulation and process development stages and to provide fundamental understanding of the granulation process. The flow properties data will be used to classify the bulk materials with respect to cohesive and adhesive properties. The data will be subsequently used to calculate the critical hopper angle and non-arching opening for mass flow to predict the flow behaviour of the powder blends and granules in the existing hoppers in pilot and production scale.

166. POWDER FLOW CHARACTERISATION OF PHARMACEUTICAL EXCIPIENTS: EVALUATION OF DIFFERENT TECHNIQUES

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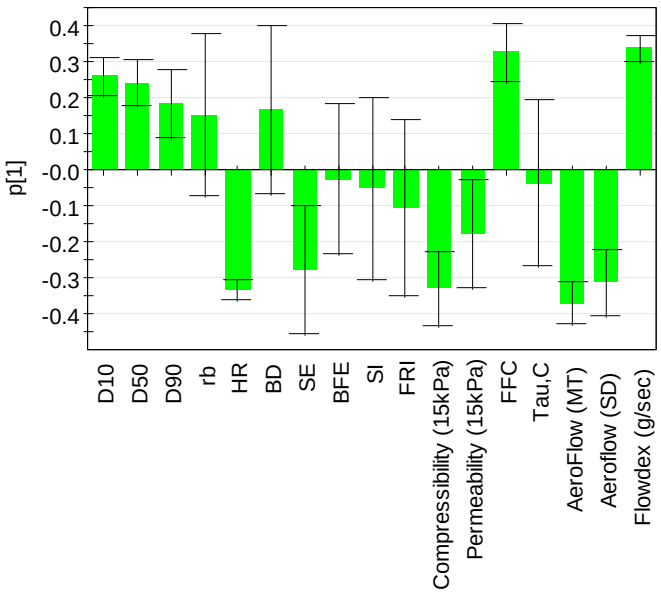
Good powder flow is a requirement for successful manufacture of pharmaceutical solid dosage forms. The main motivation for producing free-flowing pharmaceutical powders is the establishment of consistent feed from bulk storage containers into feed mechanisms of tabletting and capsule-filling machines to allow uniform packing and tablet weight uniformity. Also, there are many pharmaceutical processes that require powders to be transferred between unit operations using different methods including gravity feeding, mechanically assisted feeding, pneumatic transfer, fluidisation, and hydraulic transfer. All of these transfer mechanisms require appropriate powder flow behaviour, which is dependent on both material properties and process/transfer equipment design.

In this study, extensive work was carried out to evaluate the suitability of different flow characterisation techniques using different grades of standard excipients namely Microcrystalline cellulose, Lactose, Mannitol. The flow behaviour of these materials ranged from free flowing, to intermediate and to cohesive/poorly flowing. Seven different, powder flow characterisation techniques utilized in this study were able to give reasonably good indication on the flow behaviour for the samples showing intermediate flow properties. All of the techniques had difficulty discriminating between either free flowing or cohesive materials i.e., a given technique was able to rank differences in either cohesive or free flowing powders but not both. Multivariate analysis indicated that the ring shear tester (cohesion value), power rheometer (permeability test), FlowPro were the most suitable for describing the powder flow behaviour for the excipients studied.



Multivariate analysis of different flow measurements

167. COMPARISON OF DISCRETE ELEMENT METHOD AND POSITRON EMISSION PARTICLE TRACKING IN A PADDLE MIXER

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Most experimental measurements of internal flow are based on Positron Emission Particle Tracking (PEPT) which is based on tracking the position of a particle in a dynamic system. Recent developments in PEPT have facilitated tracking multiple particles, however its improvements in terms of achieving more representative data of the dynamics of the interested systems are not reported yet. In the present work an attempt is made to simulate PEPT experiment for a paddle mixer using DEM, with a view to investigate the effects of increasing number of tracers on their time averaged velocity distribution. The velocity information is available for all individual particles in DEM; therefore, the average particle velocity and velocity distribution of the full population of particles could be compared with individual tracers in the simulation. The results of DEM are also compared to those of PEPT experiment using a single tracer.

Figure 1 shows the average normalised velocity (average tracer velocity normalised by the tip speed of the paddles) distribution using 1-5 tracers.

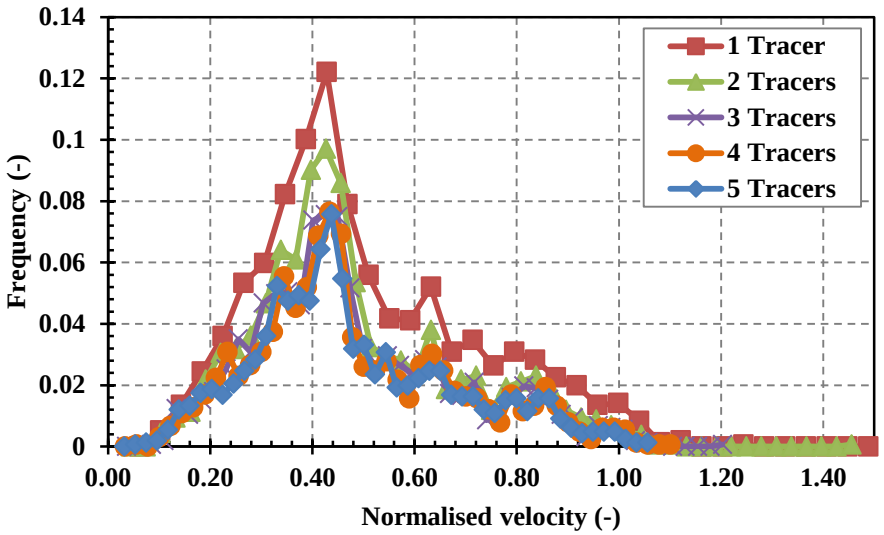

Figure 1: Average normalised tracer velocity distribution using 1-5 tracers

As it can be seen, the width of the distribution does not change with the number of tracers, however the mode of velocity is similar but its frequency changes up to the case where 3 tracers are used.

168. CONTINUOUS WET GRANULATION - A ROBUST GRANULATION TECHNIQUE FOR CHALLENGING ACTIVE PHARMACEUTICAL INGREDIENTS

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Continuous Granulation is a relatively new process for granulating pharmaceuticals, but has been used in the food and chemical industries. Cohesive and low bulk density drug substances present a number of technical challenges for formulation and process development via traditional granulation techniques, especially when high drug loading is required. For example, batch high shear wet granulation may result in bed drop within the granulator as densification takes place. This can result in poor control over the granulation process. The use of a continuous twin screw wet granulation has been shown to provide greater control and greater degree of densification in these circumstances.

A continuous granulation process was developed using co-rotating twin screw granulators at different scales of throughput (for development and commercial rates) to process a cohesive, low particle size and low bulk density Active Pharmaceutical Ingredient (API). The mechanical set-up of the granulator and feeders, effect of water and screw speed were evaluated during development work. An immediate release granule containing 70%w/w API and common pharmaceutical excipients was successfully developed and scaled up using twin screw granulation. The granules produced met the required granule critical attributes of bulk density, tapped density and flow. The use of continuous granulation allows faster and greater technical understanding of the process by using less API and resources. By comparison, when the same API was granulated by batch high shear granulation a successful and robust process could not be easily achieved. This paper discusses the development routes through both the batch and continuous methods and a comparison of the two techniques.

169. SCAFFOLDS MADE OF NANO HYDROXYAPATITE, COLLAGEN AND CHITOSAN FOR IMPROVED ADHESION AND BIOACTIVITY OF OSTEOBLASTS

Gherghe Tomoaia[1], Olga Soritau [2], Aurora Mocanu[3], Corina Garbo[3] & Maria Tomoaia-Cotisel[3]

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In this work a new strategy of syntheses is developed for silicon substituted nano hydroxyapatite with different Si contents (nanoHAP-Si) by precipitation reactions. The nanoHAP-Si of controlled porosity and crystalinity was deposited successfully on glass substrate by immersing the glass into the nanoHAP-Si aqueous dispersion. Then, scaffolds were made by self-assembling successively collagen and chitosan layers on nanoHAP-Si layer. The composite biomaterials formed of HAP-Si nano particles, mixed with collagen type I (COL) and chitosan (CHI) at different nanoHAP-Si/COL/CHI weight ratios were also designed and prepared and used for scaffolds manufacture by self assembling layer by layer technique. These biomaterials were in vitro structurally characterized by FTIR and X-ray diffractions. The BET and porosity methods were used to analyze their porous structure. SEM, TEM and AFM were also used to analyze their surface morphology and nanostructure characteristics. The incorporation of nanoHAP-Si or nanoHAP-Si/COL/CHI particles within collagen and chitosan matrix leads to biocomposites with good mechanical properties, which can be controlled by composition of biomaterials. Further, the optical microscopy, SEM and AFM were used to evaluate the behavior of osteoblasts cultured on biocomposite scaffolds for several weeks. Results showed a good adhesion, growth and proliferation of osteoblasts on the surface of biocomposite scaffolds, especially when they were made of nanoHAP-Si/COL/CHI biomaterials of 5% Si and at least 20% COL content. These data also demonstrated that the bioactivity of nano hydroxyapatite can be improved by introducing within its structure silicon. The data have revealed the high importance of shape and size of nano particles of inorganic powders in the preparation of biocomposite scaffolds of controlled porosity and mechanical properties with applications in particle technology, pharmacy and nano medicine.

170. SPRAY DRYING AS SCALE-UP READY TECHNIQUE FOR MANUFACTURE OF OXYGEN CARRIER PARTICLES FOR CHEMICAL LOOPING

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Chemical looping combustion (CLC) is a carbon capture technology where oxygen is transferred between a fuel reactor and air reactor by means of a solid oxygen carrier. In this way, direct contact between air and fuel can be avoided, and a clean CO_2 stream is generated. Currently, the critical issues for scaling up this technology are being considered. In this respect, the fabrication of oxygen carrier particles by the industrial spray drying method is under investigation.

The key issue in this application is the oxygen carrier performance, which sets certain limits to the required particles in terms of particle size distribution, density, porosity, strength, attrition resistance, cost, environmental aspects, thermodynamics and reactivity. A first generation of Ni-based oxygen carrier particles was prepared using spray drying [1]. The spray drying technique has been shown to be very well suited for preparation of oxygen carrier particles with high sphericity, high attrition resistance, good free-flowing properties, and homogeneity on the micro-scale. After the spray drying step, classification of the chamber fraction is performed. The fraction of the oxygen carriers in its green state with the correct size distribution is sintered in high temperature furnaces in order to give sufficient mechanical strength to the particles and to minimize attrition while circulating in the coupled fluidized bed system.

The toxicity and high cost of nickel has instigated a search for non-Ni based oxygen carriers with similar or superior performance in CLC. In this contribution it is shown that spray drying is a very versatile technique for the preparation of new and promising oxygen carriers with varying compositions.

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171. EFFECT OF THE ROTATION SPEED OVER THE ATOMIZATION RANGE ON A ROTARY DISC SPRAY DRYER

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The *Musa spp* is a banana cultivar that, when mature, presents high sugar content. However, when the product is still green, it presents low sugar content and a high concentration of resistant starch, which is considered as a functional ingredient due to its ability to control cholesterol and diabetes, as well as the benefits that it brings to human intestinal tract. The biomass of green banana can be used in food industry as an ingredient, in substitution to usual thickeners. The best form for commercial application is the dried product, in powder. The spray dryer is the equipment usually applied for obtainment of powder products from liquid suspensions. Once the biomass of green banana is available in pasty form, the product in powder can be obtained by spray drying the liquid suspension.

The spray dryer usually consist from a hollow drying chamber, where hot dry air is inserted on the sides. The feeding of the product is done on the upper part of the dryer, where it is atomized by the nozzle or by a disk with a high rotation. The atomization range is a very important parameter, which can influence the drying chamber design, in order to the product does not reach the wall while it is still wet.

The main objective of this work was to evaluate the effect of the speed of the disc rotation and of the height of the collector on the atomization range of the spray of green banana biomass in a pilot plant spray dryer of rotary atomizer. The experiments were performed at the Unit Operations Laboratory from the Santa Cecília University (UNISANTA). The spray drying experiments were performed in an equipment with a drying chamber with capacity for $0.2m^3$ and a rotary atomizer with 0.03m of diameter, for product pulverization. The drying process was evaluated according to a 2^2 factorial experimental design with 3 central points. The independent variables were the disc rotation and the height from the collector to the atomizer disc. The response considered was the atomization range, evaluated according to the mean atomization diameter of the green banana spray. The disk have 30 mm of diameter with 16 orifices with 3.15 mm of diameter each. The solution feed will be made with a peristaltic pump, which has a maximum flow rate of 4.35 ℓ/h.

The green banana biomass solution was homogenized with hot water in two different concentrations, in order to evaluate the effect of viscosity on the atomization range.

The green banana spray was collected on little plates covered with adsorbent material, that were equidistantly positioned over a wood support with 1.79 m of diameter, in cross from, allowing the placement of 10 collectors in each direction. An additional collector was placed under the atomization disc, in order to study whether or not there is overflow of the solution, thus avoiding the aspersion of the material.

The obtained results showed that the atomization range increased with the disk rotation, but when a determined value was achieved, the atomization range starts to decrease again due to the minimal droplet diameter. The same studies were carried out with water and calcium carbonate solution and the results of the mean atomization diameter were compared.

175. HOT-MELT COATING OF HYDROSENSITIVE PRODUCTS

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The main objective of coating pharmaceutical dosage forms is to achieve superior aesthetic quality (e.g. colour, texture, and taste), physical and chemical protection, or to modify drug release characteristics [1]. Among the coatings geared towards attaining controlled release of active principles, enteric coatings are applicable in cases where release must occur at intestinal level. Different approaches have been used to fulfil this goal, although, so far, pH-dependent systems have found practical application [2]. Most commonly used pH-dependent coating polymers are methacrylic acid copolymers [2], being applied mostly from aqueous dispersions.

The survival of a number of yeast powders (e.g. *Saccharomyces Boulardii* which is an anti-diarrhoeal agent) is challenged after oral administration, being less than one per cent of the live yeast administered orally recovered in faeces [3]. Therefore, enteric coatings emerge as an interesting alternative to protect them from gastric acidic conditions. It has been also proved that the viability of yeast cells drastically decreases when they are exposed to high relative humidity atmospheres, in combination with high temperatures [3]. Consequently, direct coating with an aqueous dispersion would lead to a loss of viable cells during the process.

In the present work, a two layer coating system is proposed to improve the delivery of *S. boulardii* to the intestine: the first layer acting as a protection barrier against moisture and the second one imparting enteric properties. For the former, hot melt coating -consisting in the application of a molten material over the substrate to be coated, followed by a solidification step upon cooling- was applied. Three different materials were selected: stearic acid, polyethylene glycol and poly(ethylene oxide)-poly(propylene oxide) block copolymers. Coating of model particles -glass beads and sodium chloride particles- was carried out in a 1 L fluidized bed. The effect of different process parameters such as the difference between bed and liquid temperatures, excess fluidization velocity, and particle and droplet size on the agglomeration rate and coating efficiency was evaluated. Special emphasis was done to establish the relationship between the behaviour of liquid droplets at micro-level and the process performance.

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176. SIMULATION OF SINTERING USING A NON SMOOTH DISCRETE ELEMENT METHOD. STUDY OF THE INFLUENCE OF TANGENTIAL FRICTION ON MICROSTRUCTURE EVOLUTION

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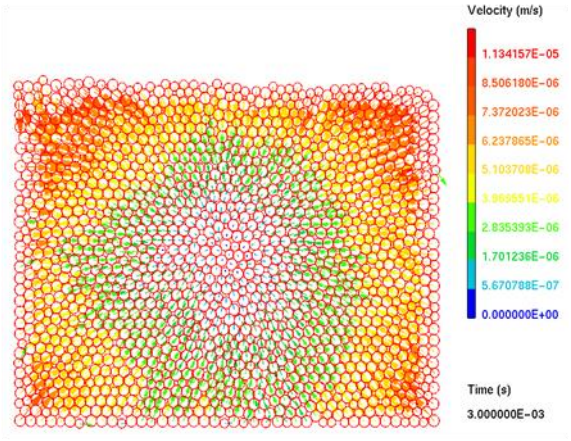
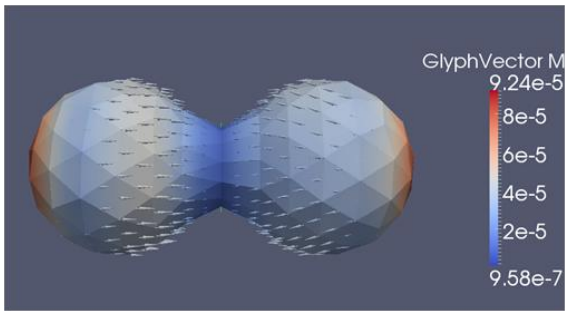
Sintering is a major process in ceramic and nuclear industries. This can be defined as the transformation of bulk materials into compact solids. The main phenomenon is solid state diffusion which occurs below the melting temperature. The physical mechanisms involved are well known but the impact of the micro-structural parameters is difficult to determine experimentally. Hence, numerical simulation becomes an essential tool to get a better understanding of the micro-structural evolution. Numerous models defined on different scales are proposed in the literature. To describe the microstructure on a pellet scale, a common approach is to consider spherical particles which overlap due to the sintering stress. Thus, this model is simple enough in order to be implemented in Discrete Elements (DEM) software that is able to handle thousands of particles.

The aim of this study is to compare a finite element simulation on a grain scale with the Discrete Element simulation. The grain scale model is based on a mechanical approach that takes into account surface, grain boundary and volume diffusion. This program has been developed for several years at the CEA. A basic sintering contact law taken from the literature has been implemented in the DEM program MULTICOR developed at the UPJV. This work should allow to improve the accuracy of the sintering contact law including new phenomena like volume diffusion or grain growth.



Sintering of 1500 particles in 2D (DEM)



Sintering of 2 particles (mechanical approach)

177. PARTICLE-DROPLET INTERACTIONS DURING THE COATING PROCESS IN A FLUIDISED BED

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Controlling drop deposition is of great importance for a wide variety of practical applications such as spray coating, pesticide deposition on plant leaves, inkjet printing, spray painting…etc. The efficiency of drop deposition from sprays is limited by two phenomena splashing and bouncing. These phenomena lead to an important decrease of the coating efficiency especially in powder coating processes. This has been shown by many studies about the wetting operation during spray coating processes (e.g. [1, 2]).

In the present work, we study the different phenomena that occur during the collision between a micro-droplet and a hydrophobic surface. The objective is to understand the effect of two kinds of parameters on the interactions between solid particles and the liquid drops in the coating process:

- the process-related variables such as the droplet impacting speed which depends on the atomizer location and the droplets size depending on the liquid and atomizing air flow rates.

- physico-chemical properties of materials used such as the viscosity of solutions and the the wettability of the solid surface with respect to the liquid.

Our experiments consist of studying the coating of different hydrophobic particles (Teflon, hydrophobic glass beads prepared by a chemical grafting treatment…etc.) by different aqueous polymer solutions .The first step of our work is studying the impact of a single micro-droplet on a horizontal hydrophobic surface and the second one is the fluidized bed coating process of spherical particles of the same nature in order to correlate the results of the impact study with the fluidized bed experiments. High speed cameras were used in the impact experiments to visualize the different phenomena that occur (spreading, total or partial rebound, splashing). The size and the speed of the droplets were calculated using a special software (i-speed). The use of a micro-droplet generator controlled by an acquisition system allowed producing droplets of known diameters and velocities. The droplets can be injected from different heights and at different horizontal positions.

The use of different concentrations of polysaccharide solutions in our impact studies showed that modifying the liquid viscosity results on the modification of droplet behaviour both at the generation and impact steps.

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178. WETTABILITY STUDY OF GLASS BEADS BED BY CAPILLARY RISE WITH PRESSURE INCREASE

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The contact angle is a very common measure of the wetability of a solid surface and is an important parameter in wet process of powder such as dissolution, dispersion, granulation, coating, drying, etc.

The hydrophilic or hydrophobic surface of the powder can be evaluated by the contact angle θ developed between three phases: liquid, solid, and vapor. In general, contact angle measurement techniques can be divided into two categories; measurement on flat plates and measurement on non-ideal surfaces or particles [1]. For flat surfaces and compact, the contact angle at equilibrium can be estimated easily by static methods using, for example, a goniometric or microscopic measurements [2]. However, the evaluation of the wettability is not easy for curved surfaces of finely divided solids. Even in the case where the particles would present ideal surfaces smooth and homogeneous, it is often necessary to indirect dynamic measurements which are based on height to balance or evolution of the mass function of time characterizing the capillary rise of liquid in the powder bed [3] [4].

Bartel et al. [5] developed a method for measuring the wettability of solids divided by the measurement of the equilibrium pressure capillary. This method is based on the application of classical models Young-Dupre and Laplace. The results of several studies [6] [7] [8] showed the applicability of this method and its potential for hosting relatively consistent information on the wetting characteristics of powders and porous media. Nevertheless, phenomena of hydrostatic and weight forces in the capillary ascension are not evaluated in several works.

The main purpose of the present study is to use of a thermodynamic and a force balance treatment of capillary rise which relate the observed pressure difference in the powder to the contact angle of the liquid on the powder. An experimental apparatus for the determination of powder wettability is described (figure 1). The technique principle is based on the measurement of variation of pressure in packed bed of particles. Tests wettability by water were performed on glass beads hydrophilic and partially hydrophobic properties with different particle size. The results were complemented and interpreted by theoretical models based on force balance.

Keywords: wettability, contact angle, capillary pressure, hydrostatic

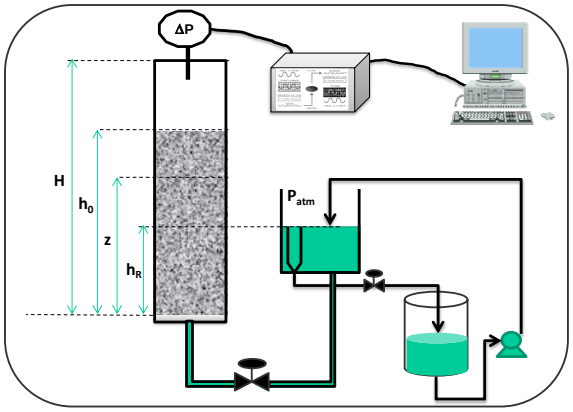

Fig. 1. Schematic diagram of the measuring system for pressure approach.

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179. ELASTIC BEHAVIOUR OF GLASSY COHESIVE MALTODEXTRIN IN PARTICLE CONTACT EXPERIMENTS

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Amorphous hygrosensitive powders are widely used in various industries like the food and beverage industry. To improve their handling properties they are often subjected to a pressure agglomeration step. The stability of the resulting compacts is thereby determined by the cohesion forces acting between small individual particles in the low micrometre range that are forced into contact. Previous investigations on the stability of agglomerates mostly focus on bulk material studies, where the strength of a compact is tested and used to theoretically predict the forces acting in individual particle contacts.

In this study, however, Atomic Force Microscopy (AFM) under controlled temperature and humidity has been employed to directly measure the cohesion between a particle and a surface of the same material as well as between two particles. The cohesive and rheological behaviour of the particles was investigated applying different parameter combinations concerning dwell time and contact force at a constant environmental temperature. In addition, the physical state, expressed in the difference between the test and glass transition onset temperature (T-T_g) of the chosen amorphous model food material maltodextrin DE 21 was varied. This was done by changing the relative humidity of the test environment and thus controlling the T_g of the hygrosensitive amorphous material in equilibrium with the surrounding conditions.

Contact tests have then been conducted on maltodextrin DE 21 samples in its glassy state, i.e. for negative values of T-T_g up to 0˚C. It could be found that changes of dwell time and applied contact force did not cause a difference in cohesion. The observed lack of creep or force curve hysteresis suggested a quasi-elastic behaviour of the material in the glassy regime. Accordingly, the applicability of a standard model developed by Dahneke [1] for cohesion between elastic substrates in contact based on the classic Hertz approach was then tested for the prediction of particle - surface and particle - particle interactions. The results can be incorporated in an existing model introduced by Rumpf [2] to estimate the tensile strength of a whole agglomerate consisting of glassy particles.

The ultimate aim is to build a quantitative and qualitative knowledge basis about the interactions between individual particles in a powder bulk that can be used to explain, predict and control the properties of a whole agglomerate.

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180. MEASURING CAKING DEGREE IN COCOA POWDERS: A MATERIAL SCIENCE APPROACH

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Cocoa powders are one of the most difficult food ingredients to handle due to its tendency to agglomerate, which is caused by the inherent sensibility of the physical state of cocoa fat. This work proposes to study the effects of temperature and relative humidity on the caking behaviour of cocoa powders. It was found that even though cocoa is able to absorb significant amounts of water at high RH%, moisture is not a major cause of caking. On the other hand, the effect of temperature on the physical state of fat was found to be of major importance and could be related to the mechanical properties of cocoa powder. Such properties were assessed by a custom made caking test fixed on a powder rheometer. Our findings are of major importance in handling and agglomeration processes involving the use of cocoa powders, and practical examples are highlighted.

181. PARTICLE TECHNOLOGY IN CONFECTIONERY MANUFACTURE

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Melted chocolate is a highly concentrated suspension of fine solid particles in a continuous fat phase. The solid particles are sugar, cocoa and milk powder. They are typically milled in roller refiners or ball mills. In the subsequent conching step, agglomerates are broken up and particles are coated with fat to obtain a free-flowing melt. The rheology of the melted chocolate is essentially determined by the size distribution of the solid particles but emulsifiers such as lecithin or PGPR can be used to manipulate particle interactions and viscsosity.

Particle adhesion forces also play an important role in the manufacture of agglomerated confectionery products. As an example, mixtures of milk and maltodextrin powder can be agglomerated in a sinter process. The mixture is hereby exposed to an increased relative humidity where the amorphous maltodextrin is in a rubbery state in which it starts to bind the particles together. When subsequently exposed to a lower relative humidity it undergoes a glass transition and fixes the sinter structure.

Alternatively, pressure agglomeration is used for the manufacture of hard candies. A mixture of amorphous and crystalline solid particles is compacted under high pressure and depending on pressure, temperature and dwell time, products of different hardness can be obtained.

182. MAPPING THE LIMITING REGIMES OF FOOD POWDER RECONSTITUTION IN A STANDARD MIXING VESSEL

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Poor reconstitution of food powders is a major quality defect that hampers the development of novel dehydrated food products. In order to improve the design of a powdered food during the development stages, an improved understanding of how the powder behaves upon rehydration is vital.

In the current study a novel approach to understanding powder reconstitution was developed. The behavior of a powder is described using a map of the limiting regimes of reconstitution, at various temperatures and agitation speeds. These regimes describe whether reconstitution was 'normal', i.e. where wetting/sinking, dispersing, and dissolving of the particles occurs readily and sequentially, or if the reconstitution process is limited by poor powder sinking, by sedimentation, slow material dissolution, or lump formation. These maps are combined with overall dissolution time measurements via conductimetry. By comparing maps for four types of maltodextrin: DE21, IT21, DE6, and IT6, the influence of particle size, material molecular weight, temperature, and agitation speed on the rehydration of a water-soluble amorphous food powder was investigated.

183. ROLLER COMPACTOR: THE EFFECT OF MECHANICAL PROPERTIES OF PRIMARY PARTICLES

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Roller compaction is a continuous dry granulation process in which primary powder is compressed at high pressure by two counter rotating rollers to produce a ribbon. The compressibility of the material plays an important role in the bonding mechanism between the powder particles and therefore influences the physical properties of the ribbon.

In this study, the mechanical properties of primary powder (Hardness and Young`s modulus) of three different materials; Micro Crystalline Cellulose, Lactose and Calcium Carbonate were measured using a nano-indentation technique. Powder fractions of the size under 212 μm were granulated in the roller compactor using different hydraulic pressures in the range of 30-200 bar.

The strength, porosity, width and temperature of the produced ribbon were measured and linked to the measured mechanical properties of the primary particles. It was found that the higher the nano-indentation hardness of the material, the lower the strength, width and temperature of the ribbons, and the higher the ribbon porosity. In addition increasing the hydraulic pressure increased the strength and decreases the porosity of the ribbons for all the materials.

184. USING THE UNIFIED COMPACTION CURVE MODEL TO PREDICT THE STRENGTH OF WET-GRANULATED TABLETS

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Tablets are a common manufacturing process in the pharmaceutical industry, however predicting the final strength of tablets created via wet granulation is not well understood. The Unified Compaction Curve (UCC), developed from roller compaction [1], was applied to wet granulation for the first time to link the wet granulation process conditions to the final tablet strength.

The UCC model was initially developed to represent the relationship between the roller compaction pressure and the tablet strength for formulations containing at least 50wt.% microcrystalline cellulose. Standard tablet compaction profiles from the study collapsed onto a single master "unified compaction curve" allowing for the tablet strength to be predicted from the roller compaction process. Recent studies have shown that the UCC is applicable to the wet granulation process, enabling the tablet strength to be predicted from the number of impeller revolutions. The model also quantitatively links the granulation conditions and stresses in the granulator for the first time. This study aims to understand the effect of the effective compaction pressure exerted by the granulator impeller on the granule properties which lead to a reduction in the final tablet strength.

Granules taken from a series of wet granulation processes (involving 1:1 microcrystalline cellulose and lactose, granulated with 5w/v% polyvinylpyrrolidone (K90) binder) were characterised to examine any changes in the granule topology, specific surface area, granule and tablet densities, and the granule porosity. Granules were selected to represent a wide range of number impeller revolutions with varying granulator liquid level (30-50wt.%), binder flow rate (130g/min and 280g/min) and wet massing time (0-10 minutes).

The number of impeller revolutions did not significantly affect the granule specific surface area or granule/tablet density. Increasing the impeller revolutions created smoother, more spherical granules. A reduction in the granule porosity was observed with increasing number of impeller revolutions. The consolidation and smoothening of the granules during wet granulation are ultimately the driving factors for the decrease in the tablet strength.

Literature data for a pure microcrystalline cellulose formulation [2] also fitted the UCC model. Hence for formulations containing at least 50wt.% microcrystalline cellulose, the UCC is a suitable model to predict the final tablet strength for a given set of granulation operating conditions.

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185. COMPARISON OF THE EFFECT OF ULTRASOUND AND AN ELECTRONIC ANTI FOULING SYSTEM ON THE AGGREGATION AND SCALING BEHAVIOUR OF CALCIUM CARBONATE BY AN INLINE TECHNIQUE

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Scaling represents a serious problem to industry. Scaling in pipes leads to an increased pressure drop and often to complete blockage. On heat exchangers it reduces the heat transfer. It may also lead to unstable operation which could result in unscheduled shutdown and loss of revenue. Calcium carbonate, $CaCO_3$, is one of the most common scale components found in oilfield production wells and surface facilities. The prediction of the kinetics of scale deposition depends on an understanding of $CaCO_3$ precipitation from solution. $CaCO_3$ exists in three main polymorphs; calcite, aragonite and vaterite. Scaling is usually associated with calcite where the calcite deposition is tenacious and hard to remove. In order to prevent potential scale problems, it is important to understand the mechanism of calcium carbonate deposition.

This paper is focused on understanding the behaviour of $CaCO_3$ scaling under different process conditions in the presence of ultrasound and an electronic anti fouling system (EAF). The novelty of this work is that an inline in-situ monitoring technique is employed to obtain real time data of $CaCO_3$ deposition on a surface. The $CaCO_3$ crystals are obtained by a standard precipitation process, and the formation and deposition of the crystals is assessed using an in-situ instrument; FBRM (Focused Beam Reflectance Measurement, Mettler Toledo). The experimental work has been designed to understand scale prevention by using ultrasound and electronic anti fouling (EAF). The scaling is characterised by measuring the rate of crystal deposition on the surface of the FBRM which, unlike mass as used by previous workers, makes this method unique. The presence of ultrasound and EAF were seen to influence the precipitation kinetics in the bulk solution and as a consequence, scale deposition was reduced in the presence of both these two methods. Therefore, controlling the bulk precipitation process can be an effective means of managing the scale rate.

186. DIMENSIONAL ANALYSIS OF MILK CONCENTRATES ATOMISATION

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The world trade in dairy powders has consistently been increasing for the last fifteen years. Therefore, there is an obvious need in the dairy industry to develop tools to optimise powder production and control powder structure and functionalities. For this purpose, it is necessary to better understand the wet agglomeration mechanisms leading to powder structuration in various processes such as spray-drying, with an emphasis on the role of process parameters (operating conditions, physicochemical properties of the inlet food matter, and process design) in the final properties of dried agglomerates [1]. Liquid atomisation, which directly influences the wetting/nucleation stage of wet agglomeration, has been identified as a crucial step in spray-drying operations: the size of final agglomerates was indeed shown to be highly correlated to the size of sprayed droplets [2].

That is why we intended in this work to focus on the role of process conditions in liquid atomisation. We carried out 148 laser diffraction measurements of the mean size of droplets produced with a bi-fluid nozzle in various process conditions (liquid and air flow-rates) at two different distances from the nozzle. Ternary mixtures of water-ethanol-glycerol, along with skim milk concentrates (dried extract ranging from 30 to 40 % (w/w)) were employed to investigate the influence of physicochemical characteristics of the sprayed liquid (surface tension, viscosity, density). Our experimental results were consistent with the pioneer work of Mandato et al. [3] regarding the predominant influence of operating conditions over liquid physicochemical properties. In addition, we showed that droplet size increased with the distance to nozzle, indicating that droplet coalescence owing to inertial effects occurs quickly after liquid atomisation at the nozzle outlet. Finally, in order to model accurately the link between process conditions and droplet size, we extended the dimensional analysis approach first proposed by Mandato et al. [3] by introducing key dimensionless numbers (air-to-liquid ratio and aerodynamic Weber number) in the process relationship. This enabled to discuss the relative influence of operating conditions and liquid physicochemical properties on the size of sprayed droplets, as a function of the distance to the nozzle.

[1] Cuq, B., Rondet, E., & Abecassis, J. (2011). Powder Technology, 208, p244-251.

[2] Iveson, S. M., Litster, J. D., Hapgood, K., & Ennis, B. J. (2001). Powder Technology, 117, p3-39.

[3] Mandato, S., Rondet, E., Delaplace, G., Barkouti, A., Galet, L., Accart, P., Ruiz, T., & Cuq, B. (2012) Powder Technology, 224, p323-330.

187. IMPROVED RETARDED RELEASE WITH FLUID BED ROTOR PELLETS

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Rotor fluid bed agglomeration technology is an appropriate method to incorporate relatively large amounts of drug substance into pellets for the manufacturing of multiparticulate drug delivery systems. Compared to drug coated inert pellets manufactured by fluid bed coating the surface of rotor pellets is not smooth exhibiting pores and interstices [1]. Therefore, a coating of those rotor pellets with a release controlling polymer is accompanied with incomplete film formation also after curing and insufficient release retardation. The aim of the investigation was an additional coating of the rotor pellets with the readily soluble, non-functional hydrophilic polymer polyvinyl pyrrolidone (Kollidone®25, PVP) to smooth the surface and to fill pores, just before coating with a release controlling ethylcellulose film (Surelease®) to guarantee homogeneous film formation resulting in sufficient drug release retardation.

The manufacturing of rotor pellets (model drug sodium benzoate to microcrystalline cellulose 4:1 w/w) was performed with a laboratory fluid bed granulator (GPCG 1.1, Glatt GmbH, Binzen, Germany) equipped with rotor bowl and the coating processes with the same apparatus but with coating chamber and Wurster partition. Process parameters were accepted from former investigations [1]. For comparison, uncoated rotor pellets and a product without additional intermediate PVP coating were investigated. The processes were evaluated due to stability, reproducibility and product yield. Pellets were investigated by homogeneity of the layer and surface properties, sodium benzoate release, particle size, sphericity and bulk density.

As expected, the rotor pellet manufacturing process led to pellets with rough surface. By coating with PVP the surface was smoothed, mean particle size increased and coefficient of variation of mean particle size was constant indicating homogeneous coating process. PVP layered pellets were coated with ethylcellulose without problems. Immediate sodium benzoate release was received with uncoated rotor pellets. Release was insignificantly retarded with rotor pellets directly coated with ethylcellulose due to insufficient film formation. Pellets with intermediate PVP coating gave pronounced release retardation and significant diminished release rate constants. By the use of an additional polymer coating the drug release from rotor pellets becomes more reproducible and may be varied in a broad range and the release kinetics can be adapted to special biopharmaceutical demands.

[1] F. Priese, T. Frisch and B. Wolf, Comparison of retarded release pellets by rotary processing and fluidized bed coating, to be published

188. DEVELOPMENT AND EVALUATION OF A NOVEL PHARMACEUTICAL EXCIPIENT BY CO-PROCESSING OF MICROCRYSTALLINE CELLULOSE AND MAGNESIUM SILICATE BY ROLLER COMPACTION

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Novel, Co-processed microcrystalline cellulose (Avicel®-PH101) – magnesium silicate composites (MCC–MgS) were prepared and evaluated as potential direct compression excipients.

Different composites have been prepared by mixing 5, 10, 20 and 50% (w/w) of MgS with MCC then processing the mixtures using roller compaction. They were then evaluated in terms of their physical and compaction properties which were compared to those of MCC, MgS, roller compacted MCC and non-processed physical mixtures of the same composition in order to better understand the effects of composition and processing. In addition, Silicified MCC (Prosolv®) was also evaluated as a reference, high performance excipient.

DSC and TGA analysis of the composites, roller compacted MCC, MCC and MgS showed no evidence of a chemical interaction between the two materials in the composites.

Scanning electron micrographs of the composites show large MCC agglomerates with a small aspect ratio and surfaces covered by small MgS particles. The composites showed a significantly higher bulk density in comparison to MCC with a percentage increase of 49.1%, 50.9%, 56.6% and 65.9% when MCC was co-processed with 5%, 10%, 20% and 50% MgS respectively.

In addition, powder flow properties; determined by Carr's index (CI), Hausner's ratio (HR) and flow rate, showed a significant improvement upon co-processing with the Co-processed composites having flowability ratings of 'good' and 'very good' flow in comparison to "poor flow" of MCC "fair flow" of the roller compacted MCC.

The compaction properties of the co-processed composites and the original materials have been analysed to determine their densification and deformation behaviour using the Heckel and Kawakita models. The compaction properties of the co-processed MCC-MgS showed a higher yield pressure than MCC, roller compacted MCC and ProSolv® which is a reflection of the brittle nature of MgS, however this did not reflect negatively on tablet hardness of co-processed composites which was within acceptable values, in addition, tablets prepared with co-processed MCC–MgS had much shorter disintegration times compared with those prepared from MCC.

In conclusion, coprocessed MCC–MgS composites prepared using roller compaction show a high potential for use as direct compression excipients.

189. PRODUCT AND PROCESS DEVELOPMENT FOR STABILIZATION AND CONTROLLED RELEASE OF MICROORGANISMS BASED ON FLUIDIZED BED TECHNOLOGY

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The constitutional effect of probiotic foods depends strongly on the cultures actually used and the number of living microorganisms in the final product form. Because of that the dosage form has to fulfil the requirement to keep the microorganisms augmentable starting from manufacturing, during storage, until delivery into the intestine.

In a case study the stabilization (also known as immobilization) of a probiotic culture (Lactobacillus plantarum) was investigated as well as the controlled release of the final product. The development of the delivery form and the process engineering for drying and controlled release coating was carried out in two sub steps. For all processing steps a modular ProCell-LabSystem fluidized bed unit (supplier: Glatt Ingenieurtechnik GmbH / Germany) was used. This equipment was set-up with different processing inserts depending on the process sequence.

The product quality of the delivery form "Microcapsul" was tested using in vitro experiments to simulate the GI-tract and living cell count.

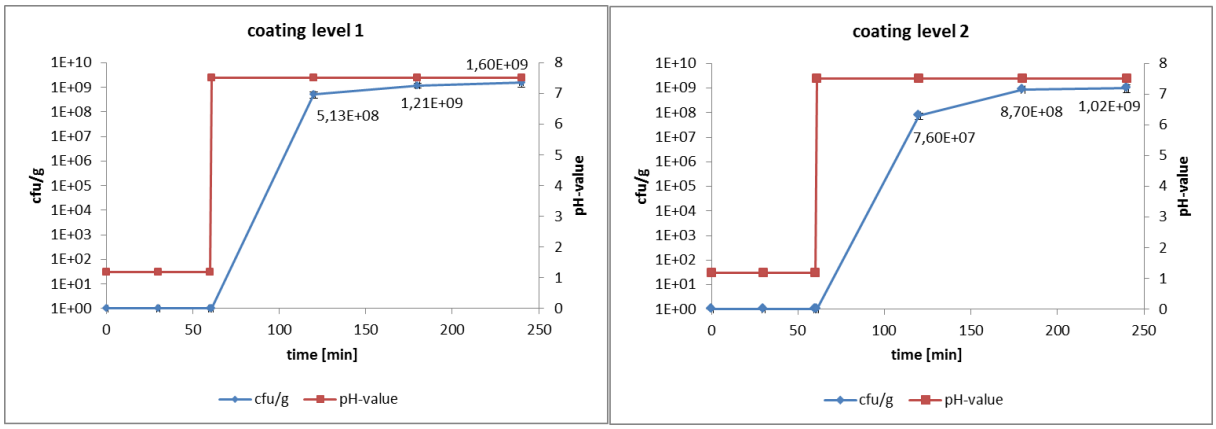

Figure 1: GI-tract-simulation; release of L. plantarum (cell count-blue) vs. pH-value (red)

Different processing options for drying and various formulations for coating were investigated and compared to each other regarding survival rate, storage stability and release in application.

As a conclusion the study has demonstrated the micro encapsulation of living microorganisms using fluidized bed technology is a promising method to treat probiotics in functional foods.

191. USE OF THERMOGRAVIMETRY AND DIFERENTIAL SCANNING CALORIMETRY TO CONTROL FREEZE DRYING OF FOOD PRODUCTS

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Freeze drying is a widely used process in the pharmaceutical and food industry, especially for preservation of active principles and nutritional quality of the substances dried. In order to avoid product degradation during freezing and water removal, in most pharmaceutical applications a specific protective matrix is often developed with the use of several excipients [1]. On the other side, this formulation approach is not suitable for food industry, where use of preservatives or additional substances is not allowed (e.g. pure soluble coffee).

In this presentation we discuss several examples about how it is possible to control the freeze drying process without modifying the initial solution composition in order to obtain the desired attributes of the final product. Freeze drying kinetics of model food substances are recorded and represented on a state diagram, which was then used to optimize a strategy to preserve the physical structure and minimize the drying time of the product.

In the first part, we compare the drying kinetics obtained in a pilot freeze dryer with the data recorded during simulation of freeze drying cycle using thermal analysis (TG-DSC). Advantages and limitation of thermal analysis are discussed, with particular emphasis on the additional information about freezing which can be deduced form the thermal signal.

In the second part we show the possibility of applying freeze-drying as structuring process. Amorphous sucrose coatings are produced, by minimizing crystallization during drying. Analysis of the physical state of the sucrose (using DSC, NIR and microscopy) showed that a dominantly amorphous coating could be obtained by carefully controlling the processing conditions. Compared to a crystalline reference, the amorphous sucrose shows faster dissolution when redispersed in a liquid.

[1] T.C. Hua, Freeze-drying of pharmaceutical and food products; CRC Press, Boca Raton, US, 2010.

192. TWIN SCREW WET GRANULATION: REGIME MAPS

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The effects of varying binder viscosity using two different screw configurations (i.e. one with kneading and conveying elements together and the other with conveying elements only) on residence time and torque and granule properties such as size, structure and strength were studied in a co-rotating twin screw granulator. In case of screw configuration with kneading elements, the increase in the viscosity of binder increased the residence time and torque. The granule size distribution reached mono-modality and their porosity decreased and strength increased at high viscosity. In case of screw configuration having conveying elements only, an increase in the viscosity of the binder also increased the residence time and torque. However, the size distribution of the granules was bi-modal. Their porosity decreased and strength increased with an increase in viscosity of binder, though in lower magnitudes. Based on the size and strength of granules produced at varying binder viscosities and screw configurations two regime maps were proposed. The deformability of granules (β) was estimated as a ratio of stress exerted on granules to strength of granules and was plotted against 'Liquid property parameter' (L/S × viscosity). In both the conditions, β decreased with increase in the liquid to solid ratio and binder viscosity. However, the magnitude of β was relatively smaller in case of screw configuration with kneading elements indicating the stronger and denser granules.

193. BLADE - GRANULE BED STRESS IN A CYLINDRICAL HIGH SHEAR GRANULATOR: FURTHER CHARACTERISATION WITH DEM

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In high shear granulation, the rotating impeller blades impart forces on the granules which are subsequently transmitted throughout the bed through inter-granule collisions. These affect the granule growth behaviour in several ways- the granules could deform, consolidate and/or break under stress, and ultimately the granular product properties.

In this work, the blade-granule bed stress in a cylindrical, vertical axis high shear granulator is characterised by DEM (Discrete Element Method) simulations. The simulations are compared and validated with the measured blade-bed stress and bed surface velocities in previous works [1, 2]. The blade-bed stresses were previously measured using a novel, custom-built telemetric impeller pressure sensor system. Following the validation, additional impeller speeds, particle/particle bed properties, impeller geometries and granulator scales cases were simulated. A modified correction factor was introduced in the blade-bed stress equation previously proposed and validated with a range of dry granule beds [1], to account for different granulator scales and blade widths.

[1] E.L. Chan, G.K. Reynolds, B. Gururajan, M.J. Hounslow and A.D. Salman, Blade–granule bed stress in a cylindrical high shear granulator: I—Online measurement and characterisation, Chemical Engineering Science, 86 (2013) 38-49.

[2] E.L. Chan, G.K. Reynolds, B. Gururajan, M.J. Hounslow and A.D. Salman, Blade-granule bed stress in a cylindrical high-shear granulator: variability studies, Chemical Engineering and Technology, 35 (2012) 1435-1447.

194. DEVELOPMENT OF APPROPRIATE GRANULATION TECHNIQUES FOR A NOVEL AGROCHEMICAL GRANULE FORMULATION WITH BUILT-IN ADJUVANT

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Liquid tank-mix spray adjuvants are often used with granular agrochemical herbicide formulations to enhance the effectiveness of the herbicide. It is however beneficial in many instances to have a "built-in" adjuvant formulation. Conventional granular formulations made from carriers such as clay, silica, starch or others have limited capacity for built in-adjuvants. Here we report on various granulation techniques such as spray granulation, pan granulation, paste extrusion, roll compaction, pellet mill etc that were screened for the development of a novel granule formulation that contains a high load of build-in adjuvant.

195. STUDY ON THE INFLUENCE OF GRANULATION PROCESS PARAMETERS ON TABLET PROPERTIES USING TRANSMISSION AND BACKSCATTERING RAMAN AND TRANSMISSION NIR

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To complete the shift from batch to continuous production in the pharmaceutical industry, the implementation of Process Analytical Technology (PAT) tools is a vital element. Therefore, this study focuses on a continuous granulation and tableting process in combination with the use of Raman and NIR spectroscopy as PAT-tools. The aim of the study was to investigate how the granulation process parameters affect the tablet properties and to verify whether Raman transmission, Raman back-scattering and NIR transmission spectra could be correlated with these tablet properties. Furthermore, it was investigated if these PAT-tools can be used to determine the hydrate level of the active pharmaceutical ingredient (API) in the tablets and if these optical measurement techniques have the same capability for API quantification in the tablets.

Granules were prepared using a continuous high shear wet twin-screw granulator (ConsigmaTM-25, GEA Pharma Systems - ColletteTM). A full-factorial design (38 experiments with 2 repeated center points) was used to study the influence of four process variables (factors): API concentration, liquid feed rate, barrel temperature and screw configuration. The granules were oven-dried for 24h at 40°C, and afterwards processed into tablets on a high speed rotary tablet press (MODULTM P, GEA Pharma Systems - CourtoyTM). Tableting process parameters were adjusted to obtain for all batches tablets with a uniform tablet weight (300mg), thickness (4mm) and diameter (9mm). From all tablets (n=72 per batch), transmission (RAMANRXN2TM Analyzer, Kaiser optical systems) and backscattering (RAMANRXN1TM Analyzer, Kaiser optical systems) Raman spectra and transmission NIR spectra (NIRFlex N-500 transmission FT-NIR, Büchi Labortechnik) were collected. Furthermore, hardness, tensile strength, friability, disintegration, apparent density, porosity, dissolution and API concentration were measured for all batches.

Principal component analysis (PCA) and Partial least squares regression (PLS) was used (SIMCA-P+ 12.0.1, Umetrics, Umea, Sweden) to model and correlate tablet properties and spectral data. For both the tablet properties and the spectral data, correlation could only be found for the API content and solid state. The influence of the other granulation process parameters on the physical tablet properties was eliminated due to the robust tableting process. Hence, predictive PLS models for disintegration, friability, porosity and tensile strength could not be established. The difference between backscattering and transmission Raman spectroscopy in the quantification of the API content was insignificant.

196. PROCESS PARAMETERS SELECTION FOR END-USE PRODUCTS AND SCALE-UP OF FLUID BED WET GRANULATION AND DRYING

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Granulation in Fluid Bed Dryers is a standard process in the pharmaceutical industry to increase powders density and granulometry for further processing (tabletting, capsule filling). This study aims at determining the critical scale-independent process parameters which impact granules properties. According to literature review [1], three variables of fluid bed wet granulation process seem to have a major effect on the final product attributes: 1- The droplet size which governs the growth mechanism, coating or agglomeration; 2- The binder concentration will influence the granules deformation and cohesion – when they are choking together – by changing the viscosity of the watering solution; 3- The maximal solid moisture reached at the end of the pulverization step, directly linked to the saturation state of the granules and which will have effects on intra-granule forces and on drying phase duration.

A DoE varying these three parameters was run at lab scale with a placebo formulation. Its statistical analysis highlighted clearly the influence of parameters on the final product attributes: low pulverization pressure (i.e. large droplet size), maximal solid moisture and high binder concentration give the best flowability, density and packing properties, essential to a good compression step. The granule size measurements all along the process indicate that granule growth rate is governed by solid moisture, necessarily well controlled. The maximal solid moisture, correlated to maximal granule size, must be controlled because the consolidation growth continues after the spraying step leading to an undesirable over-growth of granules. The end of drying period is a second critical period where granule attrition may occur: the final product moisture is governed by its isotherm i.e. by the inlet air humidity and not the drying time. Too long and not well controlled, it leads to over-drying and attrition.

The granules quality determined at lab scale can be manufactured at larger scale thanks to process parameters which are adjusted prior experiments with simulation tools and thanks to on-line monitoring tools. The granule moisture is followed all along the process using in-house software calculating water mass balance taking into account liquid flowrate and air humidity [2] and thus it can be controlled by acting on these parameters so as to reach desired maximum granules moisture and to avoid over drying. Air flowrate is adjusted to have a similar fluidisation regime according to the Künii & Levenspiel diagram and the droplet size for a given nozzle is controlled by the spraying pressure according to Walzel's correlation.

[1] B. Rambali, L. Baert, D. Thone, D.L. Massart. Using experimental design to optimize the process parameters in fluidized bed granulation. Drug Dev. Ind. Pharm, 27 (2001) 47-55.

[2] C. Gabaude-Renou, T. Politi, C. Giroud, P. Jambaud, C. Leveder, J.R. Authelin, A simple to use and inexpensive PAT tool to monitor in real-time granulation and drying parameters in fluid bed dryers, EuroPACT, Glasgow (2011).

197. INVESTIGATION INTO THE GRANULATION OF NANOPARTICLES USING SCANNING ELECTRON MICROSCOPY AND FOCUSSED ION BEAM TECHNIQUES

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Granulation of fine powder is an important process for applications such as pharmaceuticals and industrial processing, for example to improve powder flow and prevent segregation of different powder components. Primary particle size is usually of the order of a few microns. However, the mechanisms of granulation are notoriously complex, and hence a recent drive has established the importance of a physical underpinning to all aspects of granulation [1].

Nano-granulation is a relatively new field in which primary particles are nanoscale in size. In this work, both Scanning Electron Microscopy (SEM) and Focussed Ion Beam (FIB) technologies are used as a tool to directly observe some of the mechanisms involved in the granulation of nanoparticles with a viscous binder, where primary particle size is 20 - 30 nm. The resultant granules are typically 1- 100 μm in size and can have unusual morphologies. SEM is used to image the granules in various stages of formation, such as nucleation, growth and breakage. Furthermore, because the resulting granules are sufficiently small, FIB can be used to expose the internal structure. An example is shown in Fig.1, where the internal structure of a 50 μm granule shows evidence of a central nucleus, growth by coalescence and layering, compaction by consolidation and the beginnings of granule breakage. The analysis of such images provides insight into the processes occurring in nano-granulation as a function of process variables.

[1] S.M. Iveson, J.D. Litster, K. Hapgood and B.J. Ennis, Nucleation, growth and breakage phenomena in agitated wet granulation processes: a review, Powder Technology, 117 (2001) 3-39

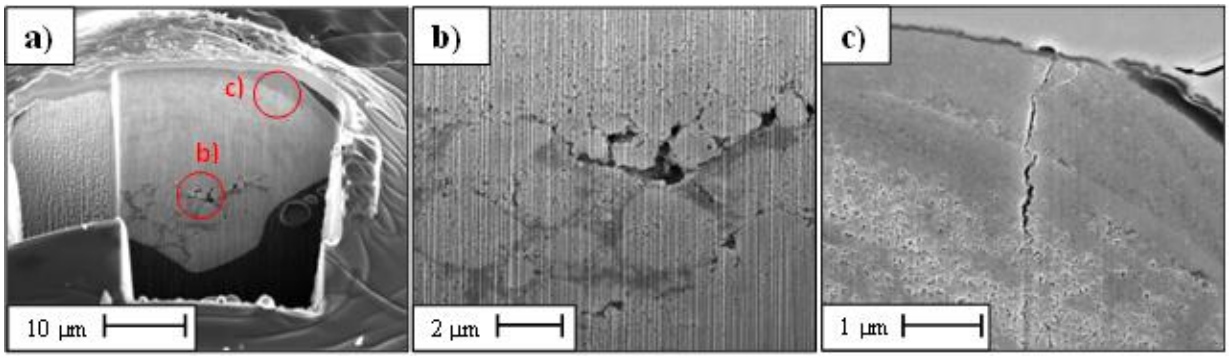

Figure 1: (a) FIB is used to mill a cross-section through a 50 μm granule. (b) The central nucleus and coalescence of several larger granules, where the darker regions are indicative of the presence of binder. (c) The surface region of the granule, where low porosity suggests consolidation. A boundary line followed by a lower porosity material suggests layering in the later stages of granulation. The vertical crack suggests the onset of breakage.

198. STUDY OF POWDER EXTRUSION ON A SMALL-SCALE EXPERIMENTAL SET-UP: INFLUENCE OF FORMULATION

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Extrusion is a very well-known process for polymers products or food products. It is a continuous process with high capacity and pharmaceutical industries have shown a growing interest on it last years. Nevertheless, small-scale studies are difficult because of the lack of dedicated devices.

In this study, extrusion experiments have been performed with an Instron® 5569 (Instron, Canton, MA, USA) universal testing machine. A cylindrical geometry has been used: a 2 cm diameter cylindrical die with a mobile punch made of stainless steel. The die is put on the structure of the Instron® instrument and the punch is attached to the moving crosshead (moving element within the load frame, which applies a load to the tested sample). A 2.4 cm diameter and 1.5 mm thickness plate with 1 mm diameter holes is fixed at the basis of the cell. For each test, a mass of 1 to 5 g of wet powder is placed in the cell, and downward-displacement of the punch was imposed. This displacement is stopped when the measured load was equal to a chosen maximal load value in order to avoid deformation of the plate. Wet powders have been prepared in a 0.5 L high shear mixer MiPro (Pro-C-epT, Zelzate, Belgium) and stored in dessicator with saturated atmospere.

The study has focus on formulation influence on extrusion process. Two types of powders have been chosen depending on their mechanical behaviour and have been tested alone or mixed in various proportions. Microcristalline cellulose was used as a plastic powder and lactose was used as a brittle powder. PVP Kollidon K30 was added as binder.

Registrations of load during extrusion have shown three steps: a first step of powder compression in order to reorganize and densify particles, a second step of steady state flow and a last step of forced flow. The key role of liquid was observed. Visual observations of extrudates have been done with SEM and porosity have been measured.

200. SCALING UP OF Na_2WO_4-Mn/SiO_2 CATALYST SYNTHESIS

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The oxidative coupling of methane (OCM) (Eq.1) is an attractive route to directly convert methane into value added compounds such as ethylene [1]. However, due to the high thermodynamic stability of methane the applied catalysts are under high demands. Thus, profitable reaction yields (>30 % C_2) over longer testing periods to be applied in industry have not been obtained so far.

$$CH_4 + O_2 \rightarrow C_2H_4 \text{ or } C_2H_6 + H_2O \quad (1)$$

Sodium tungsten manganese supported Na_2WO_4-Mn/SiO_2 catalysts has been reported as one of the catalytically most active and most stable catalyst with respect to OCM [2]. Commonly Na_2WO_4-Mn/SiO_2 catalysts have been prepared using incipient wetness method. However, various reactor types / designs for industrial scale require large catalyst batches with granule sizes bigger than 300µm. The scaled up catalyst synthesis for experimental facility for OCM process at Technische Universität Berlin (mini-plant scale) as a part of UniCat[1], is described in this work. In previous studies we could show that the fluid bed coating process (Büchi 710, Switzerland) is a suitable method to scale up the Na_2WO_4-Mn/SiO_2 catalyst synthesis [3]. Silica gels of 75-150µm were coated with finely dispersed active Na_2WO_4- and Mn-components. The catalyst showed a good and stable performance over 16h in a small lab fixed bed reactor. To be applied in the fluidized bed membrane reactor in the mini-plant larger catalyst batches of >70g per attempt and silica supports with larger granule sizes of 350-500µm are required. Thus, a larger fluid bed coating unit is under construction in our department. Spherical and irregular silica supports will be coated with the active components. Different processing parameter will be associated with the catalytic performance in the fluidized bed membrane reactor in mini-plant scale.

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201. NUMERICAL SIMULATION OF LIQUID BEHAVIOUR IN MOVING GRANULAR MEDIA USING DEM-MPS COUPLING METHOD

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In a wet granulation process, liquid binder is added to a dry and fine powder bed and the existence of the liquid can significantly influence the dynamics of the powder particles in the granulator. It is of paramount importance to understand the liquid dispersion during wet granulation as it determines the quality of the final product: fast and uniform liquid dispersion leads to narrow distributions of the granule properties, which is desirable for most of industrial applications.

In the present work, a new model is developed by coupling the Discrete Element Method (DEM) [1] and the Moving Particle Semi-implicit (MPS) method [2] so as to directly simulate the behaviour of powder particles and liquid binder. The momentum exchange between the liquid and powder particles as well as the capillary forces induced by the surface tension is taken into account for the coupling. The proposed model was applied to simulate the behaviour of a liquid droplet in a densely packed powder bed in a rotary drum and the results were compared with experimental observations. It was found that the simulation and experimental results showed a good qualitative agreement.

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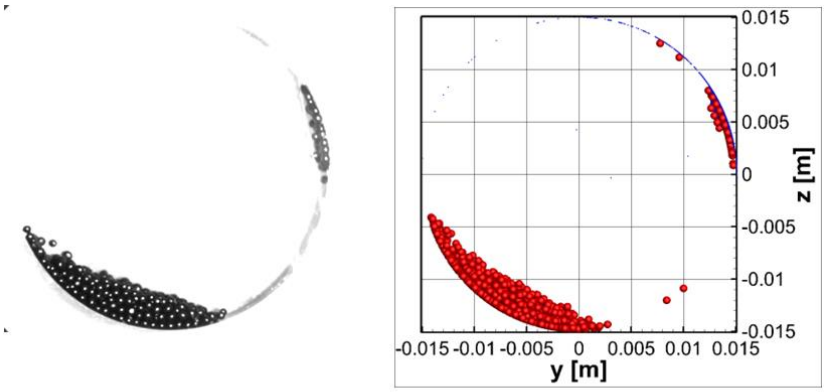

Experiment Simulation

Behaviour of partially wet powder in a rotary drum in experiment (left) and simulation (right).

202. ELECTROSTATICS EFFECT ON BED PRESSURE FLUCTUATION DURING FLUIDIZATION OF PHARMACEUTICAL PARTICLES

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Electrostatic phenomenon is a nuisance in fluidization. The arising of electrostatic charges during fluidization causes significant problems on granulation process, which include particle-wall and particle-atomizer adhesion, inter-particle cohesion and electrostatic discharges. This effect leads to significant changes in system hydrodynamics, triggering agglomeration, interference on process instrumentation, generation of electrical discharges and even explosions hazards. Particle size and shape are important factors on electrostatic charging in fluidized bed.

In this work, the pressure fluctuation signals are used to identify changes on system fluid-dynamics due to electrostatic charges in fluidized bed, using particles with different sizes distribution (150 to 600 μm), morphology and density.

The experiments were carried out in a top-spray fluidized bed loaded with particles of mean diameter of 150 to 600 μm. The fluidized bed is equipped with a perforated plate distributor with 110 mm of diameter, installed at the bottom of a slight conical piece, which is connected to a cylindrical column with 150 mm of diameter and 500 mm height. Pressure transducers connected to a PCL711-S card (Advantech) installed in a personal computer running Labtech version 12.0 software recorded pressure fluctuation time series at a frequency of 200 Hz for 2-min intervals. The bed temperature analyzed were 60 and 80 ºC, with and without water atomization Results showed that the pressure fluctuation signals changed when system dynamics were altered due to arising of electrostatic charges during fluidization, which depends on the processing parameters and physical properties of bed particles.

204. OPTIMIZING THE PROPERTIES OF BLEND FOR HARD GELATIN CAPSULES FILLING BY INCORPORATING ROLLER COMPACTION IN MANUFACTURING PROCESS

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Wet granulation is the most common method of a particle agglomeration in the pharmaceutical industry. However, there are still problems with materials, which can be destroyed by using liquids or high temperatures during drying. Moreover, it is a discontinuous batch process, so only a limited amount of material can be manufactured by wet granulation in one step. That is the reason why the roller compaction, well known and used since 19th century, experienced certain renaissance.

The aim of this work was to improve bulk density of powder formulation with nifuroxazide API and common excipients without significantly worsening of any other characteristic. The original powder mixture has been causing problems in capsule filling. The problem was solved by incorporating the roller compaction step (roller compactor Mini-Pactor®, Gerteis) in the manufacturing process. The effect of some excipients being either included in the compacted mixture or being admixed to the compacts on bulk density and flowability of mixture was tested as well as effect of roller compaction parameters. Due to this large number of parameters having the possible effect on bulk properties, a partial orthogonal factorial plan designed in statistical software for Design of Experiments (Modde 9.1, Umetrics) was used. Prepared mixtures were tested on homogeneity and segregation. Afterwards they were filled into capsules with automated capsule filling machine and their behaviour during this process was observed. The obtained capsules were tested on weight and content uniformity.

In the first set of experiments, it was found, that an additional sieving step after granulation destroys granules and worsen the bulk density. This is why was that step omitted in the second set of experiments. Generally, it was found that compression force plays the most important role in increasing of bulk density but our experience also shows that the highest force does not always provide the best result in other characteristics. Homogeneity of mixture and weight and content uniformity of capsules have improved with decreasing compression force. The gap width between the rolls has a slight influenced these properties but otherwise it determines rather the production capacity than the product parameters. Segregation tendency of mixtures was found higher in case that some excipients were extragranular and it also was affected by the compacting force. Optimizing the process and formulation parameters allowed increased production rate and quality of the capsules.

205. ROLLER COMPACTION/ COMPARISON OF RIBBON AND GRANULE PROPERTIES USING DIFFERENT TYPES OF LACTOSE

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Granulation is the size-enlargement process of particles to improve the flow-ability and compressibility of materials whilst preventing segregation. Dry granulation is a cheaper method used to agglomerate powder in different industries as no liquid is used as a binder in this process. Roller compaction is a common piece of equipment used in dry granulation, in which high pressure is applied by the two rollers to bond the primary powder particles together into ribbons, this is then, milled to make agglomerates with the desired size.

This study will investigate the production of ribbons and granules in the roller compactor using three types of lactose powder with different amorphous content , Lactose α-monohydrate 200M, anhydrous lactose SuperTab 21AN, and spray dried lactose Supertab 11SD. Effect of powder moisture content will be studied by storing the powder in different relative humidity environment prior of roller compaction. Different process and formulation parameters have been used to produce ribbons from the three types of lactose; a comparison will be then made between the properties of both ribbons and granules, in terms of porosity, strength, and granule size distribution. It was found that increasing the hydraulic pressure of the roller will increase both the tensile strength of ribbons and the mean size of granules; however, porosity of ribbon was decreasing with increasing the hydraulic pressure.

206. IN-LINE MEASUREMENT OF THE AGGLOMERATE SIZE DISTRIBUTION IN FLUIDIZED BED AGGLOMERATION

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Measurement of the particle size distribution (PSD) is a suitable way to follow-up agglomerate growth during fluidized bed agglomeration, and knowing the evolution of the PSD may give important information about the growth mechanisms and kinetics. The measurement of the PSD during agglomeration usually requires taking samples within the particle bed for off-line analysis by sieving or laser diffraction with some drawbacks. First, collection of enough powder for analysis takes time (e.g. 1 min), so sampling can not be done continuously, and the time gap between sampling represents a loose of information. Second, in most of the cases only a few samples can be taken during a trial. And third, sampling can cause a perturbation of the fluidized bed since cold ambient air may enter into the fluidized bed during sampling and collection of powder reduces the particle load. Furthermore, samples may not be representative of the whole particle bed since collected at a given point. The use of in-line probes should replace sampling, allowing continuous PSD measurement with small time gaps (down to about 1 s).

The aim of this study was to compare the follow-up of the PSD obtained by sampling and sieving and by the In-line Particle Probe IPP-70-S (Parsum, Ge) during the agglomeration of maltodextrin DE12 and DE21 particles.

Experiments were performed in a bench scale batch fluidized bed granulator (UniGlatt, Glatt, Ge), top spraying water (20 °C, bi-fluid nozzle) on 350 g of initial particles (~200 µm) fluidized by hot air with constant hot air flow rate and inlet temperature. In-line PSD measurements were performed using the In-line Particle Probe IPP-70-S, placed at a height of 8 cm above the metallic grid. Two different accessories were tested on the probe, one for keeping the optical windows free of particles (Flushing cell SZ 20-4) and the other one for directing the moving particles across the measuring zone (In-line disperser D23). The orientation of the probe (up-wards/down-wards) and the main settings (coincidence level, maximal loading) were also tested. For comparison, samples (1-2 g) were also taken along trials every 4 min and analyzed by manual sieving.

The agglomerate shape and their orientation in the measuring zone influenced the measurements done by the probe. The best correlation between sample analysis and probe measurements was found when using the In-line disperser D23 with the probe facing downwards (same orientation as the particle flow) and a coincidence level of 1.4 %.

Acknowledgements: The authors would like to thank Malvern Instruments SA for the gracious loan of the probe used in this study.

208. EFFECT OF PROCESS PARAMETERS DURING HIGH-SHEAR GRANULATION ON THE CONTENT UNIFORMITY OF RESULTING LOW DOSE TABLETS

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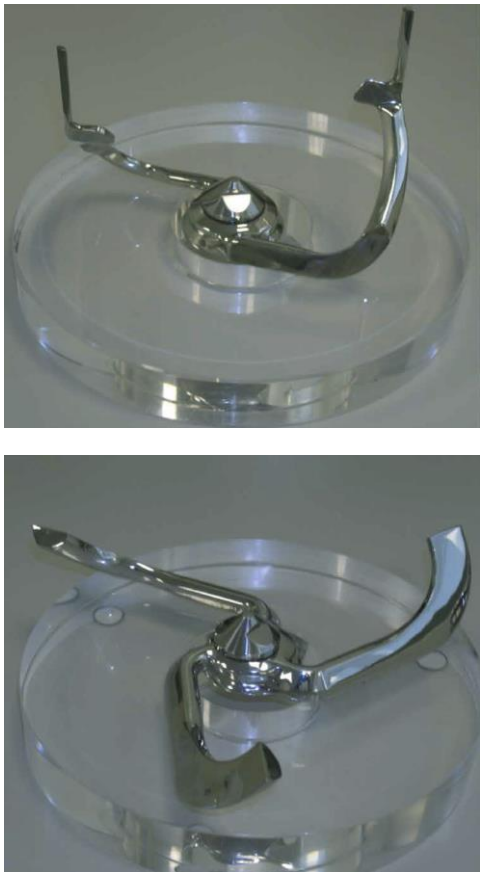
High-shear granulation is a complex process in which the particle size and hence the product properties can be influenced by process parameters as well as by design of impeller.

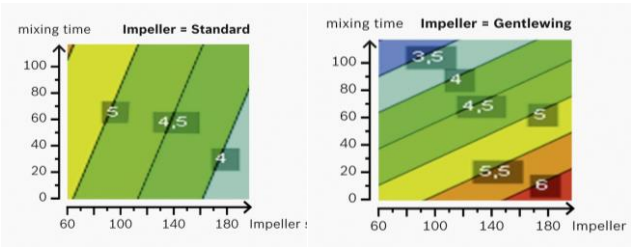
The aim of this study was to evaluate the influence of the impeller shape and process parameters on the properties of granules and tablets produced by high shear granulation. Therefore a full factorial design with five factors, two levels and four centerpoints was used. Two types of impellers were compared: the Gentlewing and the conventional 3 blade stirrer (Fig. 1a). Of particular interest was the comparison between the two mixers considering the uniform distribution of Amlodipine besilate in the tablets as well as the praticle size distribution (D50) and the compressibility index. The investigated process parameters were impeller speed, dry mixing time, water flow rate and granulation time.

The results demonstrated that the Gentlewing achieved low RSD values with low impeller speeds in contrast to the conventional 3 blade impeller (Fig. 1b). This allows a gentle appropriate granulation which can be an advantage for sensitive API's in order to avoid their decomposition. In addition the type of the impeller has no significant influence on the particle size distribution (Fig. 1c) and the compressibility index (Fig. 1d).

1a)



1b)



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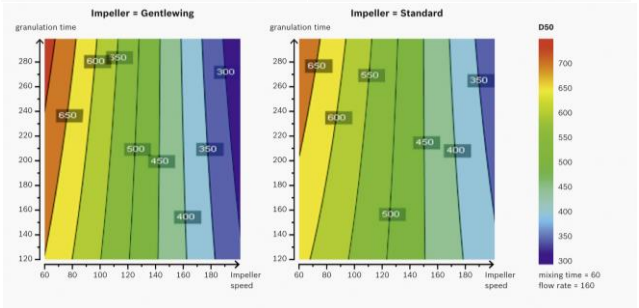
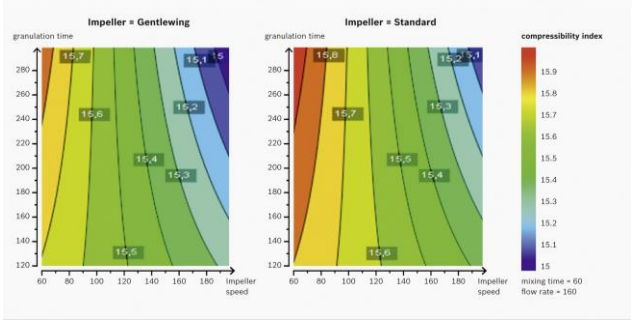


1d)



209. DEM INVESTIGATION OF HORIZONTAL HIGH SHEAR MIXER FLOW BEHAVIOUR AND IMPLICATIONS FOR SCALE-UP

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In high shear granulation, various dimensionless or dimensioned parameter groups such as constant Froude number, tip speed, relative swept volume and specific energy input are commonly used as scale-up criteria, in order to maintain the powder bed internal flow or stress field across scales. One major challenge is obtaining the internal flow and stress field through experimentation given the lack of precise measurement techniques. Therefore, this work employs DEM (Discrete Element Modelling) simulations to study the internal flow patterns and behaviour of different scale batch, horizontal high shear mixers (7 to 375 litres). The simulations provide a deeper understanding of the interaction of scale, impeller speed and fill level on the flow field, and shows that the particle velocity is correlated with the relative swept volume in these mixers. The work also demonstrates the importance of the particle size chosen for the simulation and the tool-wall gap in the mixer, and highlights its importance as we interpret DEM results.

210. A QUALITY BY DESIGN APPROACH TO INVESTIGATE THE EFFECT OF MANNITOL AND DICALCIUM PHOSPHATE QUALITIES ON ROLL COMPACTION

Nabil Souihi[1, 2], Melanie Dumarey[1], Håkan Wikström[3], Pirjo Tajarobi[3], Magnus Fransson[3], Olof Svensson[3], Mats Josefson[3] & Johan Trygg[1]

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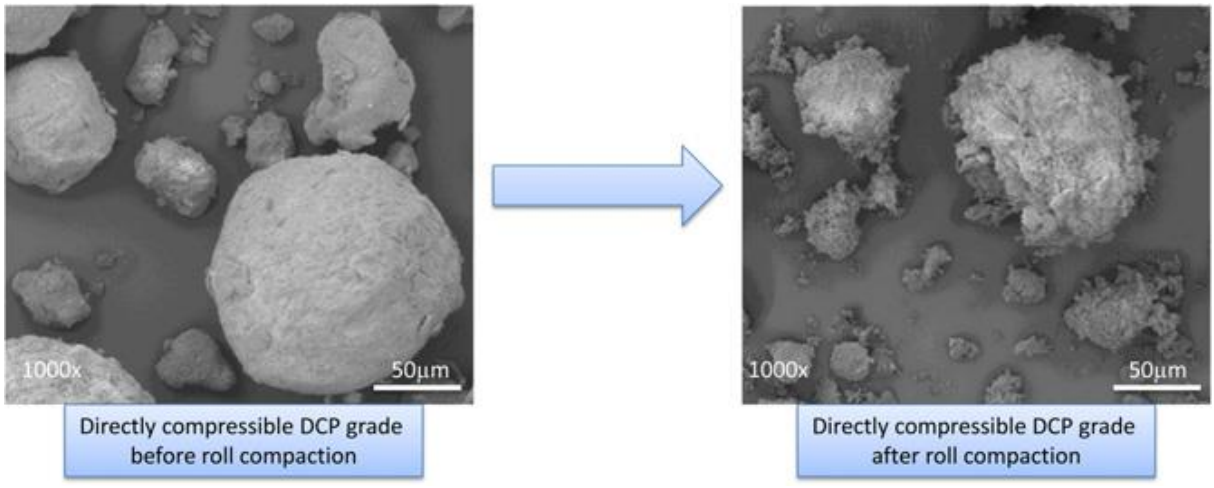
Roll compaction is a continuous process for solid dosage form manufacturing increasingly popular within pharmaceutical industry [1]. Although roll compaction has become an established technique for dry granulation, the influence of material properties is still not fully understood. In this study, a quality by design (QbD) approach was utilized, not only to understand the influence of different qualities of mannitol and dicalcium phosphate (DCP), but also to predict critical quality attributes of the drug product based solely on the material properties of that filler [2]. By describing each filler quality in terms of several representative physical properties, orthogonal projections to latent structures (OPLS) [3] was used to understand and predict how those properties affected drug product intermediates as well as critical quality attributes of the final drug product. These models were then validated by predicting product attributes for filler qualities not used in the model construction. The results of this study confirmed that the tensile strength reduction, known to affect plastic materials when roll compacted, is not prominent when using brittle materials. Some qualities of these fillers actually demonstrated improved compactability following roll compaction. While direct compression qualities are frequently used for roll compacted drug products because of their excellent flowability and good compaction properties, this study revealed that granules from these qualities were more poor flowing than the corresponding powder blends, which was not seen for granules from traditional qualities. The QbD approach used in this study could be extended beyond fillers. Thus any new compound/ingredient would first be characterized and then suitable formulation characteristics could be determined in silico, without running any additional experiments.



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[2] Souihi, N.; Dumarey, M.; Wikström, H.; Tajarobi, P.; Fransson, M.; Svensson, O.; Josefson, M.; Trygg, J. A quality by design approach to investigate the effect of mannitol and dicalcium phosphate qualities on roll compaction. Int. J. Pharm. 2013, 447, 47-61.

[3] Trygg, J., Wold, S., 2002. J. Chemometr. 16, 119-128.

211. DESIGN SPACE ESTIMATION OF THE ROLLER COMPACTION PROCESS

Nabil Souihi[1,2], Mats Josefson[3], Pirjo Tajarobi[3], Bindhu Gururajan[3] & Johan Trygg[1]

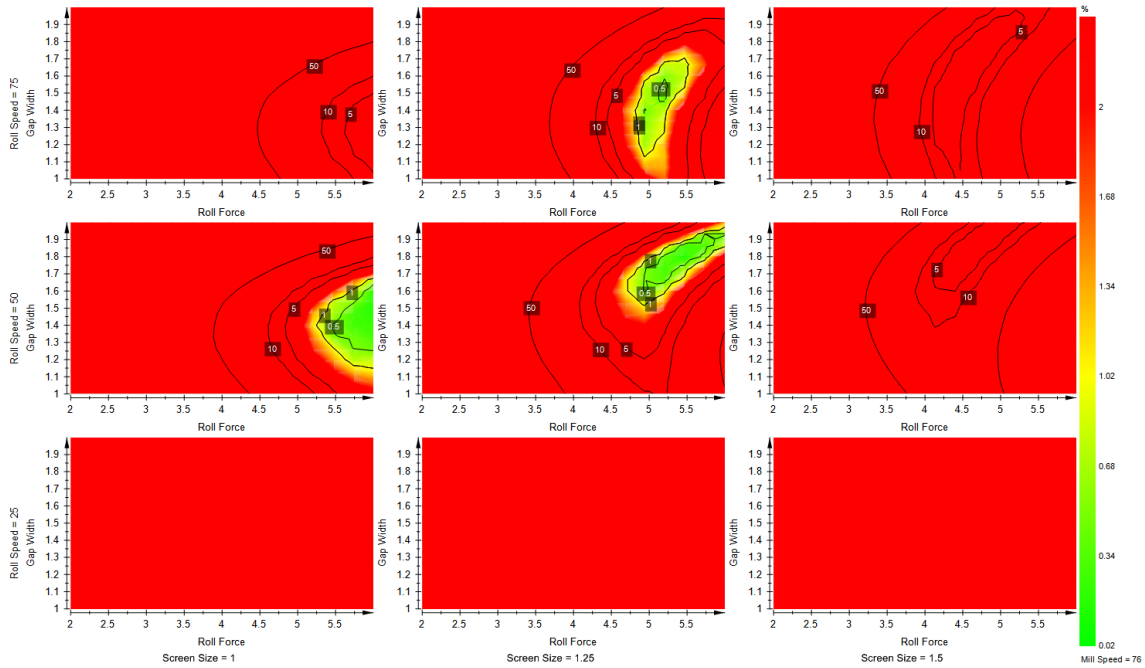
1 Computational Life Science Cluster (CLiC), Department of Chemistry, Umeå University, Sweden
2 Industrial Doctoral School, Umeå University, Umeå, Sweden
3 Pharmaceutical Development, AstraZeneca R&D Mölndal, Sweden

Roller compaction (RC) is a continuous process for solid dosage form manufacturing within pharmaceutical industry achieving similar goals as wet granulation while avoiding liquid exposure. From a quality by design perspective, the aim of the present study was to demonstrate the applicability of statistical design of experiments (DoE) and multivariate modeling principles to identify the Design Space of a roller compaction process using a predictive risk-based approach. For this purpose, a reduced central composite face-centered (CCF) design was used to evaluate the influence of roll compaction process variables (roll force, roll speed, gap width and screen size) on the different intermediate and final products (ribbons, granules and tablets) obtained after roll compaction, milling and tableting. After developing a regression model for each response, optimal settings were found which comply with the response criteria. Finally, a predictive risk based approach using Monte Carlo simulation of the factor variability and its influence on the responses was applied to estimate the design space, which fulfill the criteria for the responses in a space where there is a low risk for failure. Responses were: granule throughput, ribbon porosity, granules particle size and tablets tensile strength. The multivariate method orthogonal partial least squares (OPLS) [1] was used to model product dependencies between process steps e.g. granule properties with tablet properties. Besides the design space estimation, the results of this study confirmed that the tensile strength reduction, known to affect plastic materials when roll compacted, is not prominent when using brittle materials. While direct compression qualities are frequently used for roll compacted drug products because of their excellent flowability and good compaction properties, this study confirmed earlier findings that granules from these qualities were more poor flowing than the corresponding powder blend [2].

References:

[1] Trygg, J., Wold, S., 2002. J. Chemometr. 16, 119-128.

[2] Souihi, N.; Dumarey, M.; Wikström, H.; Tajarobi, P.; Fransson, M.; Svensson, O.; Josefson, M.; Trygg, J. A quality by design approach to investigate the effect of mannitol and dicalcium phosphate qualities on roll compaction. Int. J. Pharm. 2013, 447, 47-61.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Screen Size = 1.5

212. ASSESSMENT OF SINGLE PARTICLE CONTACT MECHANISMS AND COHESION UNDER CONTROLLED TEMPERATURE AND HUMIDITY

Christine I. Haider[1], Tim O. Althaus[2], Gerhard Niederreiter[3], Stefan Palzer[3], Michael J. Hounslow[1] & Agba D. Salman[1]

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Pressure agglomeration processes such as roller compaction and tabletting are widely used in powder refining industries, e.g. the pharmaceutical or food and beverage industry. The desired result is an improvement of the handling properties and the consumer perception of initially fine powders. Larger particle assemblies show better dissolvability as well as flowability and can be dosed and packaged more easily. They are formed when bulk material is compacted in order to flatten or break primary particles to facilitate the creation of contact points and cohesion between them. The cohesion can originate from Van der Waals interactions between flattened particle surfaces, sintering effects and liquid bridges based on capillary condensation.

Numerous modelling approaches aim to predict the result of compaction processes to design high-quality agglomerates with beneficial properties concerning their structure and stability. These quality-determining parameters are predominantly linked to the interactions between individual powder particles under the influence of the applied process conditions. This creates the need for an experimental assessment of the prevailing contact mechanisms between particles under pressure and the quantification of the resulting cohesion.

Based on this, a novel device called Micromanipulation Particle Tester (MPT) has been introduced in the framework of this project. The MPT offers the opportunity to measure the compression and cohesion forces between particles larger than 500 μm in size in experiments that comprise the application of a fixed particle deformation whilst controlling the relevant process conditions temperature and humidity, compression speed as well as contact holding time. Furthermore, the contact zone and sinter bridge growth between particles can be monitored with the aid of a digital-microscope.

MPT experiments were performed on the viscoelastic flattening and viscous sintering behaviour of amorphous spherical model food particles composed of Maltodextrin DE 21 above their glass transition temperature. A comprehensive process parameter study showed the overwhelming influence of the adjusted environmental conditions on the mechanical behaviour of the material, the prevailing contact mechanism and the resulting cohesion for a variation of set deformations and contact times. The results can be used to determine the most promising combination of adjustable process conditions to create an agglomerate with desired beneficial properties.

213. A COMPARISON OF GRANULE PROPERTIES BETWEEN IMPELLER SLASH IN HIGH SHEAR MIXER AND SCREW ROTATION IN TWIN SCREW EXTRUDER

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Granulation is a process of particle size enlargement in which particles are agglomerated while retaining the integrity of the original particles. Generally, there are two granulation approaches, namely wet and dry granulation, and the high shear mixer (HSM) and twin screw extruder (TSE) are widely used in wet granulating.

Lactose 200M and Calcium Carbonate were used in both experiments as primary particles, while HPMC was used as aqueous binder. The granule size distribution, sphericity and aspect ratio were measured by the QICPIC; while the granule strength was measured by the Zwick.

High Shear Mixer (HSM) is batch basis equipment and usually works with aqueous binder, which sprays on the powder bed surface. In the HSM granulation, the most important variables are impeller speed, binder amount and viscosity.

Twin Screw Extruder (TSE) is continuous process which allows for long-term granulation. An external pump is usually used in a lab scale TSE, which connects the pump and the compartment by an elastic pipe. The main factors that affect the granule properties are feed rate, screw speed, binder injecting rate and amount.

The aim of this paper was to find out how the process variables such as impeller, binder amount and viscosity affect the granule properties in HSM; while the screw speed and feed rate in TSE. According to the results, it was found that the granule size increased with increasing in impeller speed in HSM, while the granule size decreased with increasing in screw speed in TSE. Furthermore, the study also investigated the granule sphericity, strength and aspect ratio at different process variables.

214. MOVEMENT OF SECONDARY IMMISCIBLE LIQUID INTO A SUSPENSION OF HYDROPHILIC PARTICLES IN A CONTINUOUS HYDROPHOBIC PHASE

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Many food products are composed of suspensions containing hydrophilic particles within a continuous hydrophobic phase. An example of this type of product is peanut butter spread. Extensive work has been reported on the effects of rheological properties of suspensions with the addition of small quantities of a secondary immiscible liquid [1]. However, the kinetics involved in the movement of the secondary liquid in this process is not fully understood.

Using the inverted microscope, suspensions have been prepared to see the movement of the secondary liquid by taking a time lapse of images. These are then converted to binary images, and processed using MATLAB to quantify the increase/decrease in the secondary liquid quantity with time to better understand the kinetics involved. This is of extreme importance globally where environmental conditions vary greatly, and also during the manufacturing process, as this will ultimately affect the properties and shelf life of the end product.

[1] Koos, E. and N. Willenbacher, *Capillary Forces in Suspension Rheology.* Science, 2011. **331**(6019): p. 897-900.

215. GLASS TRANSITION TEMPERATURE EFFECTS ON THE BREAKAGE AND DISSOLUTION OF SINGLE AMORPHOUS FOOD PARTICLES

W. Robert Mitchell, Christine I. Haider, Busayo Onasile, Michael J. Hounslow & Agba D. Salman

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Many food powders consist of amorphous components that are hygroscopic and hygrosensitive; thus, their material properties can be affected depending on the conditions under which they are stored, particularly temperature and relative humidity. These changing material properties can thus influence the behavior of powders during processes such as pressure agglomeration and reconstitution. However, information related to the behavior of the individual particles under these processes is limited.

In the current study, non-porous, spherical particles were produced of an amorphous, water-soluble food material, maltodextrin DE21. A technique was developed to produce particles with different glass transition temperatures (T_g onset), between 6°C and 75°C. These particles were subjected to breakage tests by applying an external load at 22°C ambient temperature (T) at 0.01 mm/s punch speed, as well as single particle dissolution tests (at 0°C, 25°C, and 50°C). During breakage tests, particles with a $T_g > T$ were in the glassy state, and underwent a brittle fracture when the load was applied, and exhibited a higher tensile strength. Particles with $T_g < T$ on the other hand were in a "rubbery" state, and deformed when a load was applied before falling apart. Particles dissolved more quickly at higher water temperatures, and no statistically significant trend was observed in relation to particle T_g; however, the average dissolution rate decreased with increasing T_g at each water temperature tested.

The mechanism proposed to explain the increase in strength and slower dissolution with increasing particle T_g is related to a lower free volume within the amorphous matrix, resulting in a stronger intermolecular cohesion that resists both breakage and dissolution.

216. ASSESSMENT OF GRANULE PARAMETERS FOR IMPLEMENTATION IN PROCESS MONITORING AND CONTROL OF TWIN SCREW WET GRANULATION USING HIGH SPEED IMAGING

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The purpose of this study is to evaluate the feasibility of using a 3D high speed imaging Eyecon™ camera for in-line size monitoring during a twin screw granulation (TSG) process and to assess the optimum parameters for monitoring and controlling the process [1]. A critical component of any process monitoring application is sample presentation and thus a sample chute is designed (Figure 1A) to ensure unbiased sampling from a free falling granule stream during data acquisition. Figure 1B depicts a representative image that clearly captures a full particle size range, which is important in case of a TSG process because of its characteristic wide granule size distribution [2-3]. A placebo formulation consisting of lactose monohydrate (73.5%), microcrystalline cellulose (20%), hydroxypropylmethyl cellulose (5%) and croscarmellose sodium (1.5%) is used. Experiments are carried out at incremental liquid to solid (L/S) ratios to assess the ability of the camera to detect granule size changes. The sensitivity of the camera to intentional process perturbations is also evaluated by changing the L/S ratio in real-time while monitoring the process. Statistical process control tools are used to assess the implications of selecting different granule quality characteristics for detecting process shifts. The results obtained indicate the sensitivity of the camera to changes in granule size and particle count in response to variation in process parameters and the utility of control charts in comparing different quality attributes.

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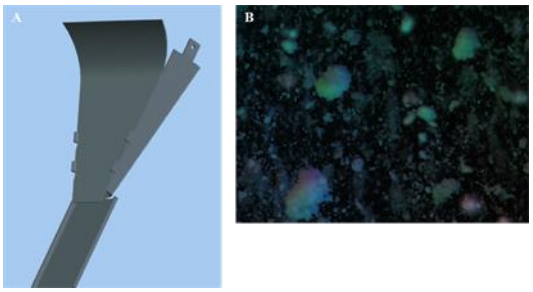

Figure 1. Design of sample chute (A) and a representative image depicting the range of granule sizes captured by the camera (B).

217. TWIN SCREW GRANULATOR: EFFECT OF PRIMARY PARTICLE SIZE

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In this study, three different size classes of lactose powder were agglomerated in a twin screw granulator under the same process conditions using 6% hydroxypropyl cellulose solution as a binder. The size distributions of the produced granules were measured and compared.

It was found that the effect of primary particle size is related to the two process parameters, screw speed and screw configuration. The primary particle size has a significant effect upon the size of produced granules when they were granulated at low screw speed and without using kneading elements in the screw configuration. Larger primary particles produce bigger granules in comparison to smaller primary particles.

Keywords: Twin screw granulator; Primary particle size; Granule size; Wetting; Screw speed; Screw configuration

218. MICROSCALE STUDY OF PARTICLE AGGLOMERATION IN FAT-BASED FOOD SUSPENSIONS: THE EFFECT OF BINDING LIQUID

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A similar concept to the one of 'wet granulation' can be applied to suspensions, where a liquid constitutes the continuous phase. In highly concentrated fat-based suspensions, such as the ones commonly existent in food products, the addition of a secondary immiscible liquid binder results in the agglomeration of particles and formation of a spanning filling network. This network gives rise to a transition in the flow behaviour of suspensions, which can, in turn, be used to create tailored-food products.

This agglomeration of particles is related to the formation of liquid bridges. The present work examines this agglomeration process on a microscale. The effect of two binding liquids with different properties (viscosity, interfacial tension, wetting characteristics) on the adhesion of a particle and a flat surface is investigated. Forces due to water and anhydrous glycerol bridges between a glass spherical particle and a glass flat surface inside purified high oleic sunflower oil were measured with an atomic force microscope (AFM), using the colloidal probe technique. Dispersions of droplets of the secondary liquid (water, glycerol) in the continuous phase (vegetable oil) were prepared so that bridges could be created once force curves were performed on top of a droplet of the immiscible liquid.

Forces between hydrophilic glass surfaces inside vegetable oil are dominated by capillary attraction when liquids of high interfacial tension and low viscosity such as water form a liquid bridge. When a high viscous liquid is composing the bridge (glycerol), a dynamic viscous interaction contributes to the adhesion leading to a higher force, which is less dependent on the volume of the bridge.

KEYWORDS

Agglomeration, Fat Suspensions, Liquid Bridges, Immiscible Liquids, AFM

219. AGGLOMERATION OF PARTICLES IN OIL-CONTINUOUS SUSPENSIONS DRIVEN BY LIQUID BRIDGES

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Several food products consist of a suspension of water-soluble particles in a continuous oil or fat phase, such as peanut butter and other types of spreads. Texture in these products is an essential attribute which is related to consumer acceptance and preference. Therefore, being able to control and adjust the structure and flow behaviour in suspensions is of utmost importance for the food industry. The addition of a secondary immiscible liquid to suspensions, even in small quantities, results in a transition from a fluid-like to a solid-like behaviour due to the agglomeration of the solid particles. By controlling this agglomeration process, the properties of the particle network can be adjusted, enabling the creation of tailored solid particle networks in food products, hence assisting food product design.

In this research, the agglomeration of solid particles dispersed in an oil-continuous phase in the presence of a secondary immiscible liquid has been investigated, on both macro- and micro-scales. Highly concentrated suspensions (40%v/v) of crystalline sucrose or glass particles in high oleic sunflower oil were used as food model suspensions. Water and glycerol were used as secondary immiscible liquid. On the macroscopic approach, the particle network formed upon the addition of the secondary liquid was assessed by monitoring particle and agglomerate size using static laser diffraction and also by means of analysing the flow behaviour of the samples. Results showed that there is an increase in the size of agglomerates and also an increase in viscosity upon addition of a secondary liquid in the suspensions. In addition, on a microscopic perspective, the behaviour of these dispersed systems and the formation of liquid bridges was analysed by evaluating the forces between individual particles using an atomic force microscope (AFM). The adhesion between a glass solid particle and a glass flat surface immersed in vegetable oil media containing different amounts of secondary immiscible liquid was measured using the colloidal probe technique. The presence of the immiscible liquid resulted in strong and long-range adhesion forces. Finally, this microscale approach is used to explain the phenomena observed macroscopically and the mechanisms that lead to agglomeration.

KEYWORDS

Agglomeration, Immiscible liquids, Fat continuous suspensions, Liquid bridges, AFM

220. EVALUATING THE SOLID SURFACE FREE ENERGY OF AMORPHOUS MALTODEXTRIN

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The formation of strong material sinter bridges between particles in industrial pressure agglomeration of powders containing amorphous substances has recently raised increasing interest. Current approaches focus on the assessment of controllable factors affecting sintering processes and the design of sintered agglomerates with a tailored internal structure. One of these factors is the solid surface free energy (γ_s) of an amorphous material, which is known to be one of the main driving forces for particle sintering [1,2]. This study focuses on determining γ_s of a commonly used amorphous food powder Maltodetxrin DE21. Two different approaches were used to determine γ_s of maltodextrin: one involves contact angle measurements on smooth maltodextrin surfaces and the other involves measuring the interfacial tension of solutions of maltodextrin. For the latter the results obtained were extrapolated to obtain γ_s at high total solids concentration.

Two commonly applied theoretical approaches were investigated for determining γ_s: the Fowkes model and the Oss-Chaudhury-Good model. The Fowkes model proved to be consistent as the results obtained were independent of the system of liquids chosen for the analysis. The results obtained show a significant variation depending on the technique adopted for determining γ_s.

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221. SEMI-SOLID BINDER DISPERSION IN DETERGENT AGGLOMERATION

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Agglomeration and spray drying are two commonly employed unit operations for detergent manufacture. Agglomeration is suited for making higher density granules containing more thermally sensitive ingredients [1]. Detergent manufacture involves the use of a semi-solid binder which is highly viscous and paste like. This study focuses on understanding the break-up of the initial lumps of paste binder and the dispersion of these binders by mechanical action of both the mixer and particles.

Experiments were conducted using sodium carbonate powder, zeolite and alkyl ethyl sulphate (AES) detergent paste. A study conducted at the interface between the powder and paste reveals that there is no movement of the paste into the powder. Microscale phenomena do not therefore have a role in aiding paste dispersion within the mixer.

The suitability of thermal imaging and high speed photography for monitoring paste dispersion in a high shear mixer was assessed. Experiments were conducted to study the influence of impeller speed, binder-solid ratio, past injection method and time on critical granule attributes with a view to building a population balance model for detergent granulation.

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