Session 1: Granulation - The Big Picture

Agglomeration at the Sharp End - Industrial Practice and Needs

D. York
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The last decade has seen an impressive growth in the research and mechanistic understanding of the agglomeration process, along with attempts to model the process. There have even been a few papers on controlling the process. However, industry is still heavily dependent on empirical process development based on available process equipment and some experientially gained mechanistic insights. The aim of this presentation will be to provide some of the everyday challenges to process development engineers and manufacturing operators in designing and operating these processes, especially when the binder is a key active ingredient. The aim being to guide future research projects and hopefully equipment design to have a greater impact on the overall application of agglomeration.

Manufacturing Pharmaceutical Granules: Is the Granulation End Point a Myth?

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The conventional moist agglomeration process can be subdivided into three unit operations:

1) dry mixing of the powder particles,
2) moistening of the powder particles by adding the correct amount of granulating liquid,
3) massing of the moistened powder bed until the "end-point".

This procedure is as old as Homo habilis using flour and water to prepare bread inspiring Homo faber to mass clay for manufacturing ceramics. For a good quality of the product, it was important to stop the massing at the "end-point" of the granulation process. The correct amount of granulating liquid was determined by "trial and error" experiments. The "end-point" was felt in the fingertips during massing. This empirical knowledge was transmitted from generation to generation. For a small-scale production of pharmaceutical granules in a lab, the pharmacy student is still taught to add to the powder mass an adequate amount of granulating liquid in order to obtain after massing a "snow-ball"-consistency of the moistened powder bed. There is nothing wrong about empirical knowledge: remarkably, the Nobel Laureates Müller and Bednorz, who discovered the high temperature superconductive, ceramic materials, compared their search with the galenical science of a pharmacist preparing the optimal formulation. In fact, there is still no generally recognised rigorous theory, which explains the phenomenon of high temperature superconductivity! In general, empirical knowledge prevails the theory. Only in the 1950's the elements for a scientific framework for the moist agglomeration process was developed by Rumpf in Germany and Conway – Jones in the UK. In the mean time, the moist agglomeration process has been described by population models but there is still no process model available, which can be used to identify the "end-point" of the granulation process. Thus taking into account FDA´s PAT (Process Analytical Technology)- Initiative [1] it is important for Homo sapiens to develop tools for a better understanding of the moist agglomeration process. It is proposed to add to the powder particles at a constant and relatively slow rate the granulating liquid in order to obtain the specific power consumption pattern of the formulation. It is important to know to interpret this pattern and to identify an "early signal" before the "end-point". Thus, it is possible to control the granulation process and to obtain a more homogeneous batch-to-batch quality.

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Solid Lipid Extrusion for the Production of Sustained Release Pellets

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In solid lipid extrusion pure lipids or pharmaceutical formulations based on solid lipids are extruded at temperatures of 5-15°C below their melting ranges. The solid fat index is > 80% at these temperatures. An axial twin screw extruder with dies of 1 mm diameter and 2.5 mm length was used for extrusion. The extrusion process is robust and smooth.

Depending on the fraction and the composition of the lipid the dissolution profile can be varied in a broad range. The drugs are released according to a matrix dissolution mechanism. Drugs can be incorporated up to approximately 70% (w/w) depending on the lipid. The solid composition is also important with respect to physical changes after the solid lipid extrusion. The aging of the lipids can influence the dissolution profile. Lipids with similar melting ranges but different compositions were compared with respect to physical changes during storage. Lipids with a narow chain length distribution of the constituting fatty acids are superior for solid lipid extrusion. For these pellets the dissolution profile during storage is stable.

Usually the extrudates are cut into small cylinders or milled in order to achieve a suitable solid dosage form. However, it is also possible to pelletise the extrudates in a spheroniser. The spheroniser must be heated to a suitable temperature. The spheronisation is facilitated by using a combination of two lipids with different melting ranges. The ratio of these lipids has to be optimised for spheronisation purposes. It is possible to achieve pellets with an aspect ratio of <1.2 and a diameter of approx. 1.5 mm. However, the spheronisation process is sensitive to variations in process variables and has to be controlled carefully.

Wet Granule Breakage in a Breakage Only Granulator: Effect of Formulation Properties on Breakage Behaviour

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Wet granule breakage can occur in the granulation process, particularly in granulators with high agitation forces, such as high shear mixers. In this paper, the granule breakage is studied in a breakage only high shear mixer. Granule pellets made from different formulations with precisely controlled porosity and binder saturation were placed in a higher shear mixer in which the bulk medium is a non-granulating cohesive sand mixture. After subjecting the pellets to different mixing time in the granulator, the numbers of whole pellets without breakage are counted and taken as a measure of granule breakage. The experimental results showed that the primary powder size, binder viscosity and surface tension as well as binder saturation have significant influence on granule breakage behaviour. The effect of these parameters on granule breakage is presented. The use of different measures of the granule mechanical strength as predictors of breakage behaviour is discussed.

Compression and Compaction of Binary Mixtures of Granules

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The response of granular materials to confined compression in terms of structural evolution and mechanical strength of compacts is of great interest in a number of disciplines. The possibility to predict compression behaviour from single granule mechanics as well as the modelling of the compression and compaction process are current problems of interest in this context. From a pharmaceutical formulation perspective, different components are normally mixed before farbrication of tablets and the compression and compaction of binary mixtures and how such relationships can be predicted are currently discussed [1,2]. However, the literature on the use of binary mixtures of granules, which have a more complex response to the compression pressure than solid particles [3], is meagre. In order to systematically build up knowledge of the properties of granule mixtures, there is a need to initially use simple model systems in terms of the particulate and mechanical characteristics of the granules.

In this paper, examples of the compression properties as well as of the compactability of binary mixtures of granules of well described model systems will be presented. In the study, granules formed from common pharmaceutical excipients were used, chosen to represent different combinations of compression properties, for example granules of similar deformation propensity but different compressibility. All granules were nearly spherical and of similar size and they were expected to respond to the applied compression pressure by deformation and densification and not by fragmentation. The compression behaviour of the granule powders and their binary mixtures was analysed in terms of the Kawakita parameters [4], often denoted 'a' and 'b'. It is hypothesized that these parameters reflect different compression properties of the granules, i.e. the Kawakita parameter a represents the total compressibility while the parameter 'b-1' represents the deformation propensity or failure strength of the granules [5]. The compaction properties were described as the relationship between tensile strength of the tablets and the applied compression pressure.

It is concluded that for the model granule systems used, compression properties of the mixture, in terms of the Kawakita parameters, and the compactability could be predicted as additive properties, assuming ideal mixing between the two components. The study will continue with more complex mixtures of granules.

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Comparison of Fibre Optical Measurements and Discrete Element Simulations for the Study of Granulation in a Spout Fluidised Bed

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Spout fluidized beds are frequently used for the production of granules or particles through granulation. The products find application in a large variety of applications, for example detergents, fertilizers, pharmaceuticals and food. Spout fluidized beds have a number of advantageous properties, such as a high mobility of the particles, which prevents undesired agglomeration and yields excellent heat transfer properties.

The particle growth mechanism in a spout fluidized bed as function of particle-droplet interaction has a profound influence on the particle morphology and thus on the product quality. Nevertheless, little is known about the details of the granulation process. This is mainly due to the fact that the granulation process is not visually accessible. In this work we use fundamental, deterministic models to enable the detailed investigation of granulation behaviour in a spout fluidized bed.

A discrete element model is used describing the dynamics of the continuous gas-phase and the discrete droplets and particles. For each element momentum balances are solved. The momentum transfer among each of the three phases is described in detail at the level of individual elements.

The results from the discrete element model simulations are compared with local measurements of particle volume fractions as well as particle velocities by using a novel fibre optical probe in a fluidized bed of 400 mm I.D. Simulations and experiments were carried for three different cases using Geldart B type aluminium oxide particles: a freely bubbling fluidized bed; a spout fluidized bed without the presence of droplets and a spout fluidized bed with the presence of droplets. It is demonstrated how the discrete element model can be used to obtain information about the interaction of the discrete phases, i.e. the growth zone in a spout fluidized bed (viz. Fig. 1). Eventually this kind of information can be used to obtain closure information required in more coarse grained models.

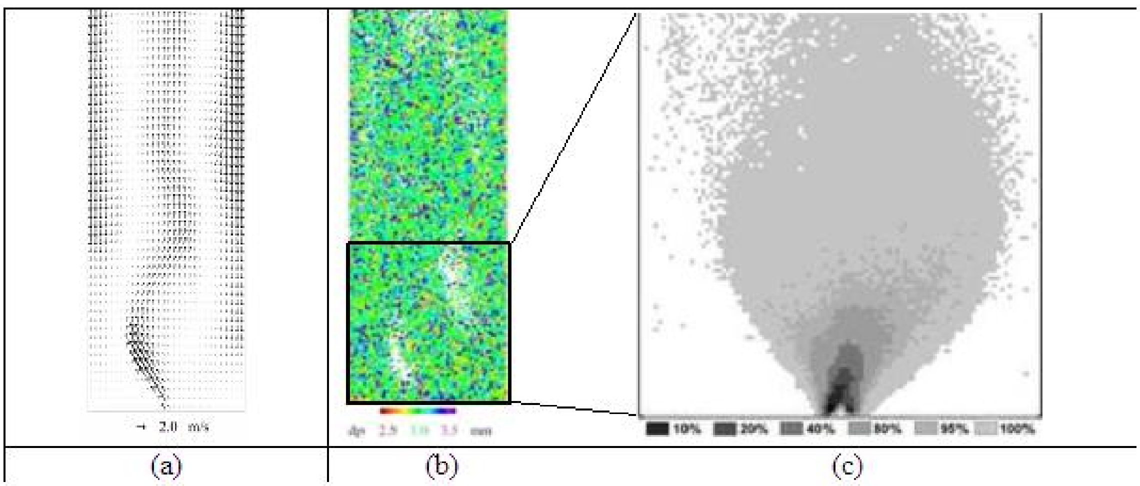

Figure 1. Close-ups of (a): the instantaneous particle velocity field, (b): instantaneous snapshot of particle positions and sizes and (c): cumulative density function of the number of deposited droplets for a period of 4 seconds predicted by the discrete element model

Session 2a: Compaction and Extrusion

Investigations on Roll Press Compaction – Interaction of Screw Feeding and Rollers

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In a roller press the bulk solid behaviour can be described theoretically by geometric parameters and material properties. The experimental verification is based on two linked approaches: The determination of the operating points as intersections of the characteristic curves of screw and rollers, and the in-line-measurement of the stress distribution in the roller gap to evaluate the influence of the feeding.

For different bulk solids and process parameters the characteristic curves of the components have been determined separately. The experimental results are compared with the models of Morning and Johanson [1,2,3]. Both theories demonstrate the importance of the pre-pressure for the coupling of the components, and thus for the dimensioning of the complete system. Depending on the parameters of both components, defined pressure-throughput-combinations are given. Knowing the feed condition, the stress distribution and maximum pressure in the roller gap can be calculated according to Johanson [2]. To verify this theory one roller is instrumented with five combined pressure-shear-sensors.

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Frontiers in Extrusion Spheronisation

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The technique of extrusion-spheronisation is routinely employed in the pharmaceutical and specialty chemical sectors to manufacture spherical granules from highly concentrated suspensions or pastes. The process involves two manufacturing steps, namely extrusion through a circular die or multiple-die plate (often a screen) to generate rods or strings of material followed by spheronisation, where the extrudate is spun on a patterned plate which causes the rods to break up and become rounded into granules. Extrusion can be performed by a number of devices, including basket, screen and conventional end-plate extruders. Given the popularity of the technique and the value of the products, the understanding of the processes and their linkage is rudimentary and the majority of process design and development is based on empirical testing. Troubleshooting extrusion-spheronisation processes for defects such as non-spherical granules (particularly dumb-bell formation) and wastage (excessive fines generation) is therefore time-intensive and expensive.

In this paper we review the physical fundamentals of the processes involved in extrusion-spheronisation and the linkages between the steps, particularly how the extrusion stage affects the shape and microstructure of granules in the spheronisation (or Marumerisation) stage. We describe recent developments in modelling of the key steps: quantitative models do exist for some of these, but in others even qualitative descriptions are incomplete so that predictive modelling is not currently available. The scope for linking models, and thereby process simulation, is discussed and we will highlight where further effort is required. Particular focus is paid to screen extruders and recent experimental evidence.

Validation of a Continuous Wet Granulation Process Using a Twin-Screw Extruder

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Due to the growing interest of the pharmaceutical industry in flexible, continuous production processes, a continuous wet granulation technique using a modified twin-screw extruder was developed at the Laboratory of Pharmaceutical Technology [1]. This technique allows to continuously process granules without any (wet or dry) milling step as the extruder is run without die plate.

The main objectives of this study were to validate this granulation process and to identify the critical parameters which determine the granule quality and its tabletting properties. Therefore, the influence of several parameters was investigated:

- The mixing efficiency using tracers added in different ways (dissolved in the granulation liquid, suspended in the granulation liquid and as a powder): the tracer concentration was determined as a function of time, as a function of granule size and as a function of the method of tracer addition. Experimental results showed that the modified twin-screw extruder is a robust wet granulation technique, where mixing efficiency is high and independent of time, granule size and tracer addition method

- The screw profile design: the screw profile had a significant influence ($p < 0.05$) on the amount of lumps (>3150 µm), yield (<1400 µm), granule friability and tablet disintegration time. Mixing efficiency was not influenced by the screw profile.

- Process parameters such as total feed rate and screw speed: the amount of lumps, yield and granule friability depended on these process parameters ($p < 0.05$), whereas tablet properties and mixing efficiency were not influenced.

Reference:

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Session 2b: Fluidised Bed Processes

Formulation and Polymorphic Screening Using a Miniaturised Fluid Bed

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Novel miniaturized techniques with precise process monitor and control systems are crucial in the challenging and expensive work of drug development. New substances, excipients and formulations need to be characterised fast and evaluated accurately as soon as possible. The concept of preformulation has become more important. Preformulation includes the use of physicochemical parameters of a drug and excipients with the goal of designing an optimum product.

There has arisen a special need to determine all kinds of process behaviour with smaller amounts of material. A Multichamber Microscale Fluid bed powder Processor (MMFP) has been developed to study the process behaviour of pharmaceutical solids. The sample size (from 1 to 100 g), adjustable air flow rate (from 0.1 to 2000 ml/s) and controllable inlet air (temperature and humidity) allows material and process characterisation with wide range of process conditions.

Novel techniques are required to facilitate the understanding and the optimisation of the problematic unit operations related to drug development. A technique of fluid bed granulation using electrostatic atomisation has been developed. Recent studies also show that solid state transformations can be detected and evaluated with MMFP. During the development process of the MMFP, also non-invasive electrostatic measurement was evaluated, which may help to relieve the understanding of the complex behaviour of pharmaceutical solids.

MMFP has also been utilised to evaluate and study the fluidisation behaviour of pharmaceutical solids. Further, the fluidisation has been connected to flowability and tabletting behaviour. Different spectroscopic tools like Raman and near infrared can be applied to MMFP. These have been used to study drying process and the importance of humidity of the process air to the process behaviour, e.g. process induced transformations (PITs). MMFP is a promising miniaturising tool for defining and evaluating the design space for a solid formulation as well as for high through put screening of formulations.

References:

[1] The characterization of fluidization behaviour using a novel multichamber microscale fluid bed. Räsänen E., Rantanen J., Mannermaa J.-P., Yliruusi J. J Pharm Sci 93 (3) 2004
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ProCell Technology: Modelling and Application

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Spouted bed processing can be considered as a special processing option in particle technology. In contrast to standard fluidized beds particles are fluidized by a gas jet in a strongly conical or prismatic process chamber.

Based on this technology Glatt has developed the innovative ProCell processing unit to carry out various processes like spray granulation, coating, agglomeration and heat transfer.

In figure 1 a schematic summary of a ProCell and its related processing steps is shown.

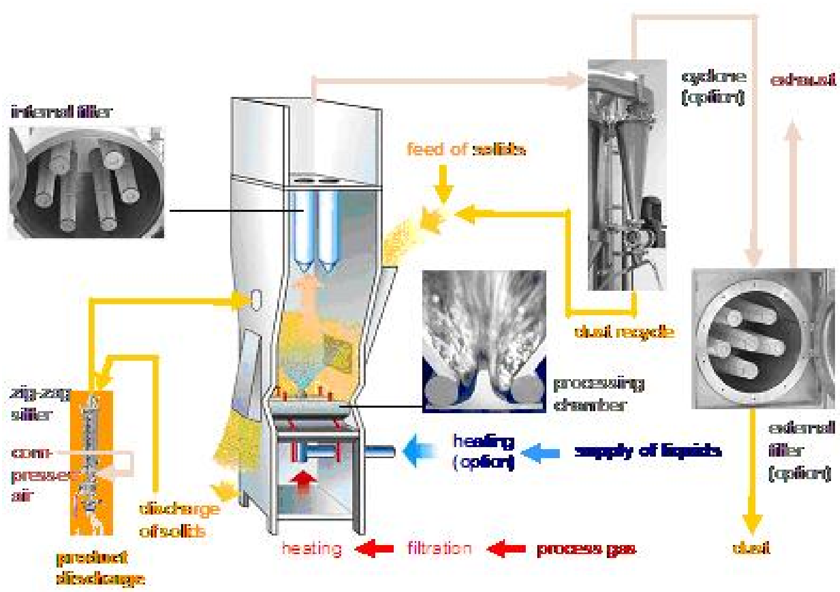

Figure 1: principle sketch of a ProCell-unit and its related auxiliary equipment

The advantages of the new technology are most prominent for the spray granulation of very fine particles, aiming for a homogeneous structure and a uniform surface.

Furthermore, coating processes involving the application of very high amounts of coating material can be carried out, because a mix of fine and large particles can be fluidized more easily in this machine than with a conventional fluidizing process.

Typical for the new technology is the special design of the process air distribution and the processing chamber. The patented design without air distribution plate results in an equipment insensitive to clogging. In addition, the specific air flow pattern inside the machine provides new possibilities of process control. Advantages compared to known fluid-bed equipment include the substantially smaller filling volume (bed mass) in the processing chamber, which improves the quality especially of heat-sensitive materials. In addition, the flow of process air in the machine results in a controlled movement of particles which provides very good conditions for the injection of liquids during granulation and coating processes.

The first part of the lecture includes an introduction into process basics and industrial examples of ProCell applications.

In the main part of the lecture results of basic research activities on fluid mechanical behaviour of ProCell – apparatuses will be explained and discussed. Studies on particle movement are shown which are simulated based on CFD using the Euler-granular approach. Additional practical experiments were done in different scales to investigate the operation window of the apparatus. Results of numerical simulations are compared with experimental observations.

A very flexible experimental set -up was installed to study the fluidization behaviour of different products at different operating conditions (Figure 2)

Figure 2: experimental setup

As model substance Al2O3 with an average diameter of 1.75 mm and a density of 1040 kg/m³ was used for experiment and simulation.

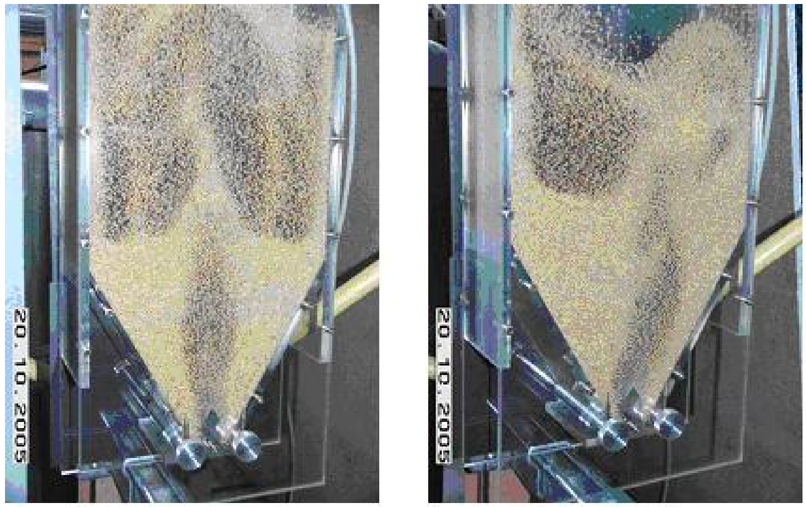

Figure 3: fluidization pattern of 2 kg particles at 151 m³/h air flow rate

Various calculations were made to simulate the fluidization behaviour and compared with the practical tests.

As an example two screenshots of CFD-modelling are shown in figure 4.

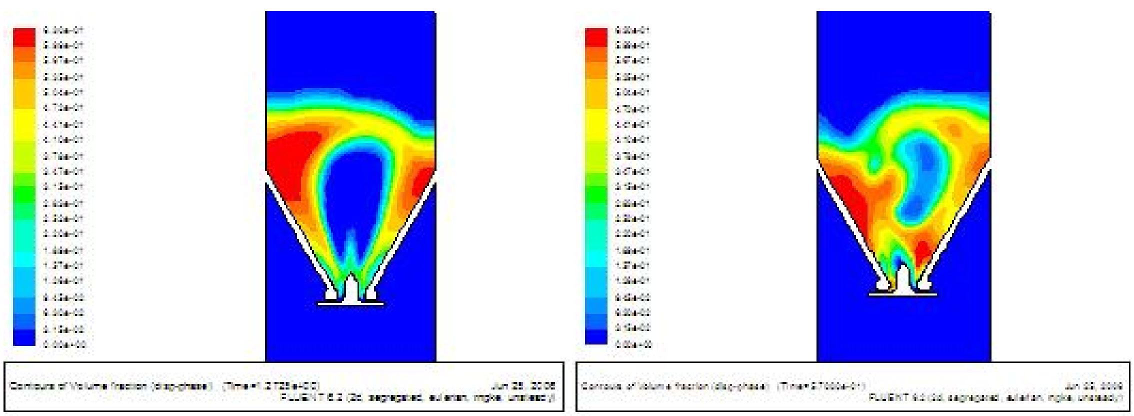

Figure 4: results of CFD- analysis

In figure 4 contour plots of solid-phase volume fraction are shown at different process times.

The lecture focuses on experiences in simulating such apparatus and discussion of conformity between experiment and model.

These studies support the understanding of spouted bed processing using the ProCell apparatus and allow sensitivity studies and technical optimisation.

Towards a Complete Population Balance Model for Fluidised Bed Spray Granulation: Simultaneous Drying and Particle Formation

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In the literature, many attempts can be found to describe the particle formation in fluidized bed granulation in terms of population balances, which describe the temporal change of number distribution. The particle formation in fluidized bed granulation is influenced be numerous parameters. Watano et al. [1] observed that the moisture content in the solids is one of the most relevant particle properties to control the granulation process. This leads to the conclusion that the properties (here particle size and moisture content), which control the process of particle formation, should be considered in the population balance model. Consequently a multidimensional population balance model is needed.

The presentation concerns the coupled processes of granulation and drying. In order to predict temperature of the gas and the solid phase and moisture content in the solid phase, heat and mass transfer mechanism and particle size enlargement have to be combined in one model. Therefore the solid phase is modeled by a three dimensional population balance with internal coordinates size, enthalpy and moisture. The numerical simulation of such high dimensional population balance systems is very demanding. The model reduction using marginal distributions is one possibility to overcome these numerical problems. The latter leads to a coupled set of three one dimensional PBE, which contains kinetic expressions for heat and mass transfer between solid and gas phase. A first attempt for this kind of model reduction was done by Hounslow et al. [2], who extended the vector of internal coordinates by the particle tracer mass. The resulting 2D-PBE was transformed into a set of two 1D-PBE assuming that particles of the same size contain the same amount of tracer mass. Tan et al. [3] applied this model to fluidized bed melt granulation. The more general case of liquid spray granulation can not be found in literature.

It will be demonstrated, how the processes of granulation and drying can be described in heterogeneous fluidized bed model taking material properties such as adsorption isotherms into account. Further it will be shown, that the discretization scheme of Hounslow et al. [2] for multidimensional population balance will fail to predict intensive properties of the disperse phase. Therefore a modified discretization, which preserves the mass and the number of the system as before and predicts the intensive properties such as particle temperature and particle moisture content, is suggested [4]. For the better understanding of the processes some simulation results for evolution of particle size distribution, change of particle enthalpy, change of particle moisture contents, outlet and mean gas temperature and outlet and mean gas moisture contents, will be presented. The model is then used to predict the results of the experiments (Figure 1).

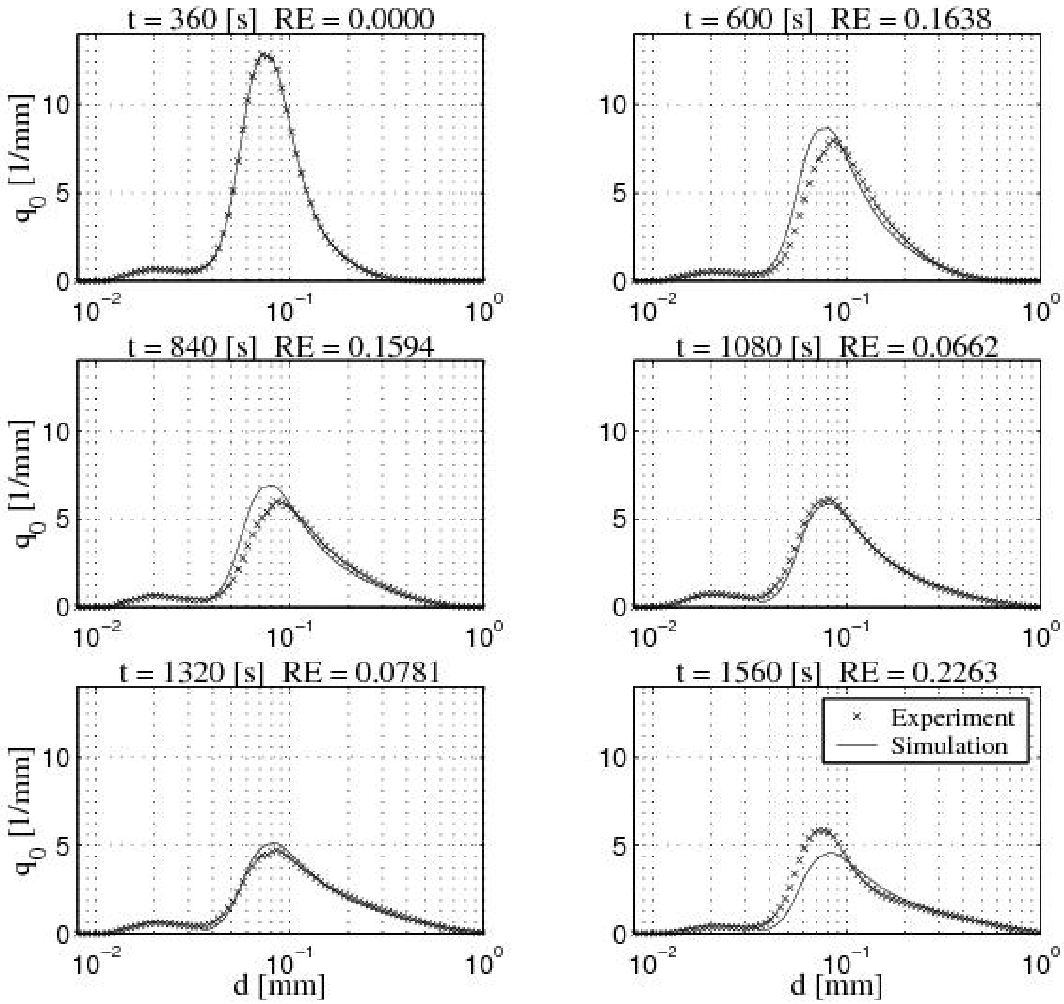

Figure 1: Comparison of measured and simulated PSD

References:

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Session 3a: High Shear Processes 1

Motion and Mechanisms in High Shear Mixers Using Positron Emission Particle Tracking

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High shear mixers are used in many industrial application for wet granulation processes. An integral component in the understanding of granulation fundamental mechanisms such as nucleation, growth and breakage, is the powder flow behaviour within granulators. The fundamental motion and mechanisms of powder flows are complex and poorly understood as there are no universally excepted constitutive equations for granular flow and the sensitivity of the flow to equipment geometry [1].

An investigation was made into the flow behaviour of dry and cohesive powders within a vertical high shear mixer, using Positron Emission Particle Tracking (PEPT). The complexities of the powder flow are observed for a variety of formulation properties and operational parameters. Data on particle position, local velocities, accelerations, particle density and strain rates presents a detailed view of powder behaviour. Applications for modelling granulation processes in high shear mixers using compartmentalised models of PEPT data are also reviewed. This paper is the second presentation of complete particle motion behaviour in rapidly-stirred solids. The objectives of the work are to produce a comprehensive "map" of particulate motion, to understand the effects of operating parameters on granulator performance, to devise better monitoring and end-point determination, and to improved designs of granulators.

Reference:

[1] Litster, J. and B. J. Ennis (2004). The Science and Engineering of Granulation Procsses, Kluwer Academic Publishers.

Particle-Particle Coating in a Cyclomix Impact Mixer

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Dry particle coating has been used to create new-generation materials by combining different powders exhibiting different physical and/or chemical properties. Materials with relatively large particle size (host particles) can be mechanically coated with fine particles (guest particles) in order to create new functionality or to improve their initial characteristics. The coating of a host powder by guest particles can be performed in many different ways ranging from simple stirring of two components, to high energy impact coating.

The purpose of this work is to study the surface modification of silica particles coated with magnesium stearate by dry coating. The coating experiments were performed by using a high shear mixer granulator called Cyclomix and manufactured by Hosokawa Micron. The Cyclomix can be used for a number of processes: granulating, coating, agglomeration, etc. Large particles of silica (median diameter, 55 µm) were coated with fine particles of magnesium stearate (median diameter, 4.6 µm) at different concentrations.

Different methods of characterization were used to study the physico-chemical properties of the coated particles. The uncoated and coated particles were observed by scanning electron microscopy (ESEM). The magnesium stearate has been softened and smeared over the silica gel particles. The wettability was determined by measurements of the contact angle between the coated particles and water. The moisture adsortion-desorption isotherms of uncoated and coated particles have been characterized. The results showed that the moisture resistance of silica gel powder was improved after coating by hydrophobic magnesium stearate in Cyclomix.

It has been demonstrated that the Cyclomix can be used for the dry particle coating to modify the properties of silica gel powder.

A Narrow Size Distribution on a High Shear Mixer by Applying a Flux Number Approach

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Recent work of Michaels and Hapgood has shown that by controlling the solids flow regime in a high shear mixer, and by reducing the binder flow rate, an improved control of the particle size distribution can be achieved. The present work seeks to confirm this by applying a flux number approach, similar to previous work by this author on fluidised bed granulation. Indeed good control over the particle size distribution can be achieved, but independent distribution parameters, such as d0.1, d0.5, and d0.9, cannot be controlled individually, as they all depend in a similar way on the process conditions.

Encapsulation Process: A Way to Produce Dry Water!

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Nowadays, there is a strong need for consumer-friendly products in powder form such as unit-dose products or rapid dissolution formula. They have to be easy to handle and should display a good stability upon storage. It is crucial to master the different stages of particulate processing and to understand the mechanism of particle association at a microscopic level in order to satisfy these demands and optimize the performances of the products.

Water-rich powder containing up to 98% (by weight) of water and characterized by the same flow properties as dry powder was prepared by two mixing processes, a high shear mixer and a planetary mixer. Each particulate consists of a microscopic water droplet surrounded by a network of self-associated hydrophobic fumed silica particles. Once the network is created, the formed shells are strong enough to withstand external stresses. The conditions leading to the formation of water-rich powders strongly depend on the silica particle hydrophobicity.

Highly hydrophobic powder may be used in high shear mixer in which liquid is portioned into small droplets under high turbulence. Under the same conditions less hydrophobic particles leads to a foam kind of final product. From theory we assume that the energy brought to the system may overcome the energy of emergence of less hydrophobic particles. Then the particles are brought inside the liquid phase and interact with each other to form a continuous path leading to the formation of foam.

In a planetary mixer less hydrophobic particles produce water rich powder similar to the one obtained with usual high shear mixer. Under the same conditions highly hydrophobic particles are useless. In this process, water droplets are created by single fluid liquid atomisation and brought in closed contact with a dense cloud of solid particles. For highly hydrophobic particles the adhesion to the liquid interface is less favourable and may be overcome by kinetic energy leading to the rebound of the particles without any shell formation.

This study reveals that depending on solid phase characteristics the processes has to be well adapted in term of wetting energy. Under this condition, water-rich powder can be easily produced on an industrial scale.

Session 3b: Pharmaceutical Granulation 1

Fluidised Bed Granulation of Pharmaceutical Materials: Characterisation using Raman Spectroscopy

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This study investigates the granulation of pharmaceutical materials in a co-melt fluidised bed system. Experimental data on the effect of process parameters on granulation such as: formulation; particle size; binder viscosity and gas flow rate, are presented. These data are subsequently correlated to granule growth mechanisms and the quality of the product granules. Furthermore, this study proposes an important new use of Raman spectroscopy, which allows in-situ measurement of the composition of the material within the fluidised bed in three spatial dimensions and as a function of time. This is achieved by recording Raman spectra from specific volumes of space. 2-dimensional Raman mapping of solid samples is well established and the employment of confocal Raman microscopy in this study allows 3-D mapping of solid materials within the fluidised bed. The technique has the potential to give detailed in situ information on how the structure and composition of the granules/powders within the fluidised bed vary with the position and evolve with time.

Nucleation and Granulation of Hydrophobic Powders

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Granulation of hydrophobic powders is a growing problem in the pharmaceutical industry. The structural complexity of new drug molecules mean that is increasingly common for entire classes of drug compounds to be highly hydrophobic. This creates considerable difficulty in understanding, controlling and trouble-shooting these industrial granulation processes.

There have been many recent advances in granulation theory (Litster and Ennis, 2004), but it is assumed that wetting and spreading of the fluid through the powder particles is a prerequisite for good granulation. The possibility of a fine, hydrophobic powder spreading over the surface of the liquid during nucleation has been identified theoretically based on surface chemistry (Rowe, 1989) and as a potential nucleation mechanism (Hapgood 2000, Simons and Fairbrother, 2000). Recently, investigation confirmed that nucleation can occur by spreading of the sub-micron particles around the template drop (Farber et al., 2006). This unique nucleation behaviour, called "solid spreading nucleation". The hollow granule structure formed by the solid spreading mechanism is unique and suggests the possibility of using the controlled, open granule structure to manufacture "designer pharmaceutical particles" with advantageous properties:

1. Controlled granule size by manipulating the size distribution of the spray drop "templates"
2. Controlled granule structure by exploiting the solid spreading mechanism.

This allows for the potential for designer pharmaceutical particles, with controlled size distribution and excellent ideal flow and handling properties. This paper will describe single drop solid-spreading nucleation experiments where single fluid droplets are placed onto loosely packed powder beds of hydrophobic powders and the formation of the powder shell observed via high speed video camera. Experimental results and observations for a model system will be presented.

The Effect of Powder Flow and Die Fill on Tablet Properties

I.C. Sinka [1], F. Motazedian [1], A.C.F. Cocks [2] and K.G. Pitt [3]

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The preferred drug delivery system today is represented by tablets, which are manufactured using high speed rotary presses where the powder material is compressed in a die between rigid punches. Compression represents one of the most important unit operations because the shape, strength and other important properties of the tablets are determined during this process. These properties are dictated not only by the characteristics of the powder constituents, but also by the selection of process parameters imposed by production machinery. This paper focuses on the die fill and the compaction steps.

Die fill on high speed rotary tablet production presses is a complex phenomenon. On most presses the powder is deposited into the die under the effect of the gravity. The process is facilitated by force feed from paddle wheels in the feed frame and the suction effect, whereby the lower punch is withdrawn while the die opening is exposed to powder in the feed frame. An experimental shoe-die system was developed to examine the effect of the contributing factors. High speed video observations enabled a detailed examination of the die fill process. The flowability of the powders was quantified using the concept of critical velocity. It was illustrated how a detailed understanding of the die fill process could contribute to the design of powder feed mechanisms as well as selection of press parameters in order to ensure consistent and efficient die fill, thus maximising the productivity of the presses.

The process parameters (such as the effect of punch velocity, dwell time, compression stress, pre-compression, compression position in the die) during compaction are discussed with reference to tablet strength. Results generated using a compaction simulator as well as rotary tablet presses are presented for a range of pharmaceutical excipients and placebo formulations.

Mechanistic Based Prediction of Granulation Output Through Multidimensional Population Balances and PAT Sensors

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Wet granulation in high shear mixers is an important process step used in the development and manufacturing of pharmaceutical oral solid dosage forms. In recent years, the pharmaceutical industry has increased its efforts in the area of real time process understanding. This effort has been supported by FDA´s Process Analytical Technology (PAT) initiative.

In this study a multi-dimensional population balance model is applied to a wet granulation process of pharmaceutically relevant material, performed in a high shear mixer. Particle volume distribution, liquid saturation, liquid to solid ratio and porosity of the granules can all be modelled.

Different process monitoring techniques with respect to mechanisms on a particle-particle level are compared. The indirect technique used is monitoring the Power Consumption and the direct techniques characterized are Near-Infrared (NIR), Raman and Focused Beam Reflectance Measurements (FBRM). Information on a mechanistic level of the wet mass particle properties is extracted from the different measurements during the process evolution.

This presentation demonstrates the usefulness and potential of mechanistic process models coupled with advanced Process Analytical Technology (PAT) tools in the prediction of high shear wet granulation process output.

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Session 4: High Shear Processes 2

Scale-up and Control of Binder Agglomeration Processes – Batch and Continuous

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This review describes scale-up of granulation processes where a liquid binder is added to fine powder in order to form a granular product, with specific emphasis on the comparison and contrast of batch and continuous processes. The technical goal of scale-up is to maintain similarity of critical product attributes as the production scale and/or throughput of a manufacturing process is increased. In this paper, a scaling framework is developed to consider critical process transformations in relation to the desired product attributes. A similar approach can be taken in developing process control strategies.

In any agglomeration process, transformations can be used to describe how raw materials (typically fine powders and liquid binders) are converted into a granular product. While critical product attributes may be characterized on the scale of individual granules (e.g., size, shape, porosity, mechanical strength, etc.), industrial scale-up requires predictive relations for the sizing, design and operation of larger-scale process equipment. Considering scale-up on the basis of transformations is one way to link the macro-scale equipment decisions with micro-scale product attributes. This approach can be applied to the scale-up of batch and/or continuous granulation processes as well as transitioning from small batch prototypes to continuous production circuits. Additionally, a framework for the description and analysis of continuum flow and stress fields in mixer-granulators and the implications for scale-up of granulation processes are discussed.

Effect of Granulation Scale-up on the Structure and Strength of Granules

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Abstract Not Yet Available

Detecting and Measuring Nucleation in High Shear Granulation

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Particulate processes are of great importance in industries like chemical, agricultural or pharmaceutical industries [1]. High-shear granulation is commonly part of the solid product design chain. Consequently, there is a growing interest for this process. A wide range of end-use properties can be modified thanks to this method (flow-ability, dissolution rate, composition, particle size etc.). However, the number of granule properties changing with time makes it difficult to control. In addition, it involves several phases (solid, liquid, gas). The properties analysed during the process are usually limited (size, strength, porosity), the evolution of the liquid phase distribution being rarely measured. Consequently the nucleation mechanism resulting from the interactions between the liquid binder and the primary powder is poorly understood. This observation has led us to focus our attention on the liquid phase behaviour during the early stage of the process.

A study has been performed on industrial compounds provided by AstraZeneca. Several samples were withdrawn during each granulation batch. The particle size distribution (PSD) and the liquid content were measured. Optical microscopy coupled with Image Analysis was used to determine the PSD, because of its accuracy on small size particles. A liquid tracing procedure was implemented in order to quantify the liquid content. The impacts of the water addition technique, of the drop size distribution [2] and of the impeller speed [3] were investigated.

The results reveal the occurrence of a layering phenomenon inducing a binder content distribution with size. The competition between the different mechanisms (nucleation, aggregation, breakage) is also discussed. Finally, it is planned to use a 2-D model and simulate this experimental data in order to estimate the mechanistic kinetics of the process.

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Freezing the High Shear Granulation Process

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Various high shear granulation studies have shown that the granule properties (e.g. size, composition) are already frozen to a large extent during the first minute of the process. Unfortunately, there is still lack of detailed information about this initial stage of granulation. By literally freezing the granulation process with liquid nitrogen an investigation was done on the early seconds of the high shear granulation process. This revealed that three different processes determine the granule formation: binder dispersion, liquid penetration and granule breakage. When liquid comes into contact with the powder bed, penetration of the liquid into the powder bed can result in the formation of granules. However, impacts of the mixer arm will disperse the binder liquid, which counteracts the penetration. The balance between the penetration and the dispersion rate determines the ultimate mechanism of granule formation. Real-time measurements of the initial seconds of the granulation process showed that in case of good wetting abilities of the binder, penetration is the predominant process. This liquid penetration leads to the formation of granules in the first seconds of the process. Once these granules have been formed the strength of the granules determines whether they are broken down by or survive the shear forces. If the penetration becomes too slow with respect to the binder dispersion (high viscosity or poor wetting) complete binder dispersion will occur.

A qualitative and quantitative representation of the nucleation behavior and the relevant rate process will be presented in order to illustrate to what extent nucleation on influenced by process and formulation variables.

Session 5a: Industrial Granulation

Aspects of Industrial Granulation

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In general, the intention of granulation processes in chemical industry is to achieve certain product properties. The requirements are specific for each product and cover application properties, process and handling properties, safety characteristics and marketing features. Customers want constant application properties and flexible adaptation to new requirements.

Research in granulation aims at understanding and describing the physical processes involved. The investigations are often focused on describing the influence of process parameters on product properties or the optimization of a process step concerning a certain product property. They are usually based on a given piece of equipment and do not take characteristics of the apparatus into account. Material used for this investigations are often model systems.

These investigation are a good basis for understanding and improving granulation and product properties by modification of operational parameters of a given process carried out in comparable equipment. However, selection of an agglomeration process and equipment to be used for production is usually influenced by other factors than product properties: Options are often limited, because equipment which was used for another product is available, or the granulation process has to fit in the total production process. Moreover, the products are often more complex than model substances, and one has to deal with e.g. wide particle size distributions, several components, change of raw material quality, change of recipes or a limited choice of auxiliary agents such as binders.

In mixer granulation, only little information about scientifically based classifications of different apparatus and the differentiation of alternative granulation processes such as compaction or fluidized bed granulation can be found in literature. Therefore, one focus of industrial investigations in granulation is on comparison of different processes and assessment of different types of apparatus. Here, an example for a comparison of different granulation processes with respect to product properties will be shown.

Influence of the Material Properties on the Agglomeration of Food Particles

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Various studies investigate the influence of process parameters on the agglomeration of ideal model substances. Often obtained results are only partially valid for real food powders because of the great influence of the material properties on the agglomeration process.

In the current study the influence of materials properties like hygroscopicity, hygro-sensitivity, liquid capacity, wettability and the impact of the mechanical particle properties were investigated. It was found that physical material properties are determined by the chemical, supra-molecular and microscopic structure of the particles to be agglomerated. Thus, the structure of milk powders, vegetable powders, powdered sugar syrups and maltodextrines were analysed by methods like differential calorimetry, mercury porosimetry and scanning electron microscopy. Based on the results the behaviour of these particles during fluid bed agglomeration and tabletting are discussed. In addition, their tendency to show undesired agglomeration phenomena like caking or post-hardening of agglomerates can be predicted.

In this sense the current study tries to close an existing gap for food powders between the process specific knowledge and the material sciences.

<u>Process Parameter Analysis and Process Understanding – Some Industrial Examples</u>

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2) Budapest University of Technology, Hungary

The most modern equipment in the Pharmaceutical Industry are highly computerised and involve the possibility of process parameter statistical analysis so give the chance to get deeper process understanding. Although the standard user-software of these modern equipment do not include an intelligent data processing interface, if you solve the problem of process data handling by e.g. a spreadsheet program, you can mine out very important and interesting information. We show an example to demonstrate the importance of pre-phase (e.g. preheating) in Pilot size and Industrial size regarding scale-up problems. Some statistical analysis of process parameters are introduced in fluid bed processing and film coating highlighting the variation of different parameters and including moisture and enthalpy balance calculations.

<u>Determination of the Drying Conditions of Sticky Food Powders in a Spray Drier</u>

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Spray drying is a common technique applied to many products to obtain solids. Often an integrated agglomeration step is incorporated. Many food stuffs are spray dried nowadays. Several food stuffs show a difficult drying profile and some of these are very difficult to dry. Difficulty in drying shows by material deposition on parts of the dryer and may cause severe blocking of the dryer and connected fluid beds.

Stickiness is a phenomenon that reflects the tendency of moist powders to agglomerate and/or adhere to contact surfaces. Stickiness occurs at points where the structure of the amorphous powder changes. Humidity and temperature have a big influence on that. Also the composition, surface viscosity and the operating conditions of the dryer influence the stickiness.

This paper will focus on drying of a complex mixture of salts and nucleotides in an industrial dryer, where the operating conditions of the dryer were determined by measuring stickiness zones of the products. Relation between temperature, relative humidity, composition, pH and even seasonal differences are determined and explained.

Session 5b: Pharmaceutical Granulation 2

A Comparative Study of Compaction Properties of Binary and Bilayer Tablets

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Bi-layer tablets have been developed to achieve controlled delivery of different drugs with pre-defined release profiles. However, the production of such tablets has been facing great difficulties as the layered tablets are prone to fracture along the interface of the two layers during the compaction. Thus, knowing the interaction and bonding behaviour between different substances during compaction is of fundamental importance to better understand the failure mechanisms of bilayer tablets and the compaction behaviour of normal matrix tablets that are generally made of multiple components. In this talk, the compaction behaviour of binary mixtures and bilayer tablets of two common pharmaceutical excipients, Microcrystalline Cellulose and Lactose, is investigated. The effects of the concentrations of mixture compositions and compaction pressure on the compression behaviour of binary mixtures and bilayer tablets are also explored. The mechanical properties of binary and bilayer tablets of same compositions are also determined and compared. It has been shown that how the compositions were mixed before compaction has a significant impact on the compaction properties.

Binder Spreading and Wetting Phenomena in Granulation Processing

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In the wet granulation process, wetting interactions between the droplet and the particles are a key initial stage of the granulation process. Wettability is a therefore a significant parameter in granulation and is determined by the surface tension and capillary forces in the growth regime, as well as by the surface energies of the solids.

In the case of pharmaceutical crystalline solids many of which require granulation, their surface chemistry and thus wetting behaviour, have been found to be face specific, resulting in a more complex and heterogeneous surface than has been traditionally expected.

Despite the clear importance of binder spreading phenomena as apart of the granulation process, this subject has received very limited detailed study.

In the current work, both the equilibrium and kinetic spreading behaviour of selected binder solutions has been explicitly experimentally measured for series of model and real world solid state materials.

Single Drop Behaviour in a High Shear Granulator

G.K. Reynolds [1], V.A. Chouk [2], M.J. Hounslow [2] and A.D. Salman [2]

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2) University of Sheffield, UK

High shear wet granulation initiates when a liquid drop comes into contact with powder. As the drop makes contact with the powder, it will be subjected to a shear force which may cause it to deform or break. The resultant droplets will collect particles, defining the properties of the initial nuclei granules. It is the properties of these initial nuclei that will influence the properties of the subsequent granules in the mixer. In this work the high-speed images are used to calculate the relative velocities between a single liquid droplet and the powder surface of a 10 litre high shear granulator in order to quantify the shear imposed upon the drop. It is found that the relative velocity of the droplet with respect to the powder surface decays exponentially, consistent with the relative velocity decay of a particle experiencing drag in a liquid. Additionally the relative velocity is found to vary with relative impeller position leading to a difference in the shear forces applied to the droplet.

Microscopic Interpretation of Granule Strength in Liquid Media

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2) University of Cambridge, UK

3) University of Sheffield, UK

This paper reports experimental studies illustrating the effects of partially wetting liquids on the mechanical strength of model granules composed of autoadhesive polystyrene particles. The liquids were prepared by mixing different amount of isopropanol with pure water to vary the wetting characteristics of the test liquids on polystyrene. These characteristics were determined from measured contact angles on the polystyrene surface and the surface tension of the mixtures. To determine the granule strength, they were immersed completely in the liquid media and subjected to diametric compression. The strength parameters such as Young´s modulus and yield stress of the granules were inferred from the compression data using elasto-plastic contact mechanics theory. It was found that there was a gradual reduction in the granule strength once a "critical" isopropanol concentration is reached. Based on the hypothesis of Ottewill and Vincent (1972), it was proposed that there was preferential adsorption of isopropanol molecules onto the polystyrene particle surfaces. The exposed hydroxyl group of the alcohol molecules then form hydrogen bonds with the water molecules in the solution phase. This causes surface hydration of the granules such that repulsive solvation forces, resulted from the restructuring of the water molecules, counteract the autoadhesive forces between the constituent particles

causing a reduction in granule strength. Moreover, existing micromechanical models correlating macroscopic granule strength to the constituent particle packing and properties were evaluated by comparing the predictions with strength parameters measured in air only. The comparison demonstrated the importance of accounting for the stress amplification by pores or defects and non-uniform stress transmission in the granules for a realistic strength prediction.

Reference:

[1] Ottewill, R. H. and Vincent, B. (1972) Colloid and surface chemistry of polymer lattices. Part 1 – Adsorption and wetting behaviour of n-alkanols. Journal of Chemical Society – Faraday Transactions I, 68, 1533-1543.

Session 6: The Micro Scale - Granules and Smaller

Reactive Binders: Wettability and Adhesion Behaviour in Detergent Granulation

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Linear Alkylbenzene Sulphonic acid (H-Las), known in short as Las acid, is a surfactant used as a reactive binder in industrial detergent granulation processes. It is a reactive binder, in that it reacts with alkaline sodium carbonate particles to generate Sodium Linear Alkylbenzene Sulphonate (Las-Na), one of the world´s largest used anionic surfactants. The reaction neutralises the H-Las to increasing degrees depending on the amount of acid reacted to form the salt. Hence, during granulation the binder has the dual function of forming physical links between the particles and participating in the neutralisation reaction to form the Las-Na along with some water. Hence, the characterisation of the wetting and adhesive behaviour is complicated by the strong dependency on the kinetics of the binder-powder reaction.

The aim of the study reported here is to achieve a better understanding of the wettability and adhesive force behaviour of Las acid as neutralisation progresses in order to establish the relationship between the binder phase changes and granule formation and growth. The micromanipulator system developed at UCL has been used to carry out experiments on Las acid liquid bridges between glass particles. Since Las acid will react with alkali at the solid-liquid interface, the experiments were carried out using inert particles and acid that had been pre-partially neutralised with the alkaline powder.

It was found that the higher the degree of neutralisation the lower the tendency of the liquid to wet the particles. In particular, the lower neutralised binders (Hlas and Las-Na 30%) "jump" on the particle as soon as the contact is made, whereas increasing the degree of neutralisation only the contact area is wetted and the liquid does not spread further on the glass, i.e. the energy of cohesion is higher that the energy of adhesion. Moreover, at high degrees of neutralisation the binder behaves as a sticky paste, forming long threads instead of liquid bridges and the wet area is not uniform and circular. Finally, wettability of all the binders has been found to be strongly dependent on relative humidity (RH). These results suggest first that, under process conditions, the "wetting and nucleation" (where the liquid binder bridges on contact with the dry powder and distributes evenly between the particles) could only occur if the neutralisation reaction is below 40-50%. Moreover, the strong dependence of the wetting behavior on RH highlights the importance of controlling the environmental conditions, not only during the granulation process, but also the storage of the materials.

Surface and Wetting Analysis: An Insight into the Products of Granulation

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2) Nestlé, Germany

Granulation is currently an important part of the food manufacturing process. At present for a new product, binder selection takes excessive amounts of time and is dependant on trial and error. Being able to predict final granule properties like granule strength, porosity and size distribution prior to the granulation process would save companies both time and money, as it would avoid this trial and error phase. It is even more important to the industry with the recent implementation of PAT regulations.

Surface Energy and liquid wetting analysis can be used to give insight into the binder-powder selection part of the granulation process. It can also be used to predict which binder-powder combination will give the most desired results. The liquid wetting rate of various binders wetting powders and granules were determined. The powder-binder interactions were changed by altering the binder type, viscosity and surface tension. The wetting rates were obtained using the Washburn technique and a developed novel optical imaging technique. Granule strength, porosity and size distribution of granules produced by High Shear Granulation of the corresponding binder-powder combinations were then compared. A strong relationship between liquid wetting rates and granule strength, porosity and size distribution was found. Better wetting powder-binder combinations were found to produce stronger, less porous granules with a more narrow size distribution. The effects of wetting is less pronounced as the high shear granulation time increased.

Mechanistic Modeling of the Formation and Dissolution of Multi-Component Granules

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Computational methodology for realistic three-dimensional simulation of the formation of multi-component granules consisting of primary solid particles with arbitrary shape, size, and surface wettability, will be presented. The method is a generalisation of previous work [1], and is based on the simulation of random packing of primary particles coupled with spreading and solidification of a liquid binder. The effect of binder viscosity, primary particle size, shape, and surface wettability, and the particle collision sequence on the granule microstructure will be systematically investigated. The generated granule structure will then be subjected to virtual dissolution test [2] and the relationship between granule structure and the release profile of active ingredient determined. The structure-dissolution correlations then form the basis of a computer-aided design methodology [3], whereby the optimum set of formulation (composition, primary particle size, binder content) and processing (ingredient addition sequence) parameters is determined so as to obtain granules with a specified release profile of the active ingredient.

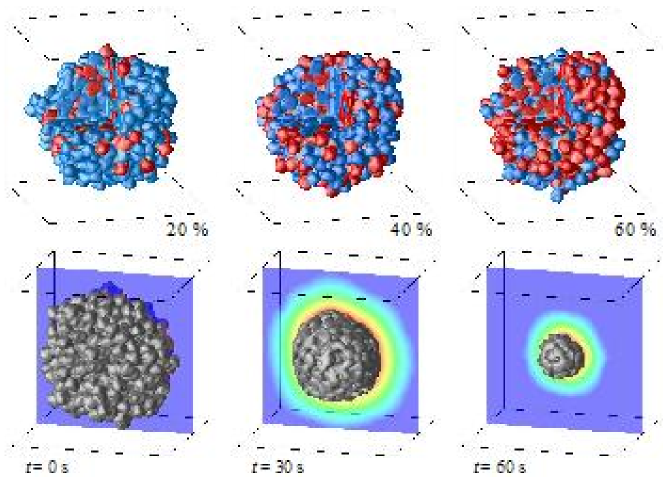

Figure 1: Example of computer-generated binary granules with varying composition, and the simulation of a single granule dissolution.

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