9th International Symposium on Agglomeration and 4th International Granulation Workshop

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Analysis of the velocity and porosity distribution in fluidised beds using non-intrusive optical measuring techniques

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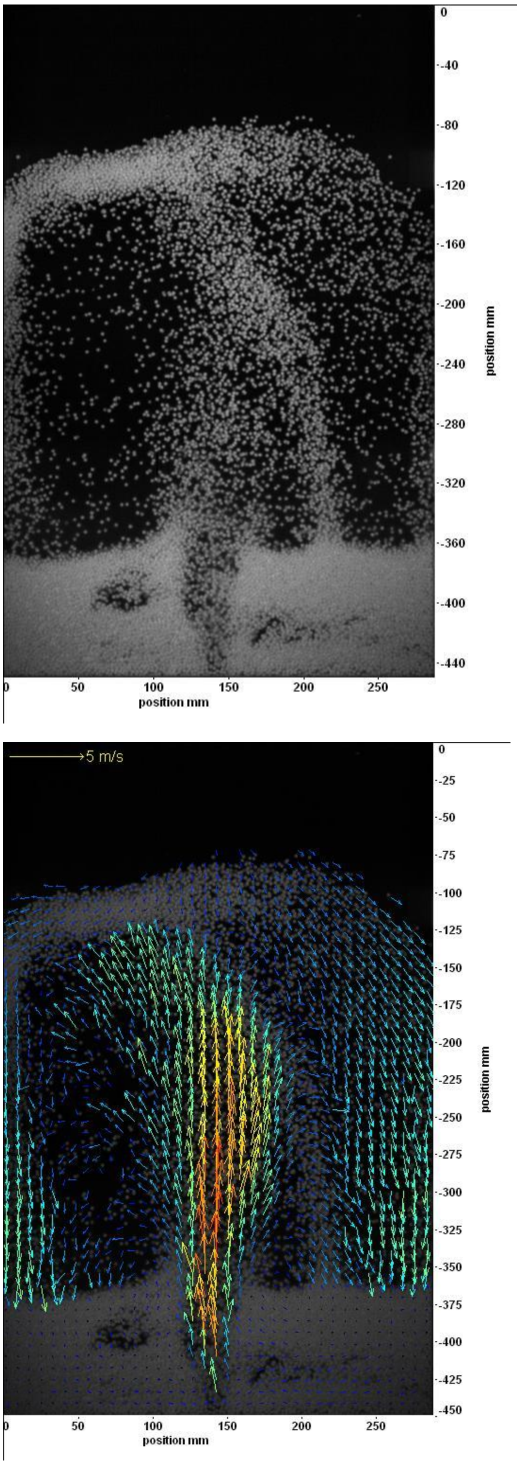
Fluidized beds are widely applied for the production of granules or materials in chemical, pharmaceutical or food industries. The fluidized bed process offers many advantages, such as an intensive contact between particles, droplets and gas resulting in an excellent heat and mass transfer and high mobility. For granulation different, types of fluidized beds are used like bubbling or spouted beds or special granulation systems with internals such as jets, injectors or Wurster tubes. However, the understanding of complex phenomena in the process is still poor concerning the residence time, the particle flow behaviour and the hydrodynamics during granulation. For the investigation of these parameters two different non-intrusive optical measuring techniques, particle image velocimetry (PIV) and digital image analysis (DIA), are employed giving a more detailed insight.

The PIV is used to obtain the particle velocity field in the bed. The resulting digital images are analyzed by means of an improved digital image analysis algorithm (DIA) which was introduced by Link [1] to estimate the porosity and the corresponding solid volume fraction fields. In this study new calibration techniques are developed by adjusting defined porosities and bed measurements with a fibre optical probe. The experimental investigations are conducted in a multi-adjustable pseudo 2-dimensional apparatus in which different types of fluidized beds can be realized. In further investigations the mean residence time and the particle circulation rate in the spout, annulus and fountain zone of spout fluidized beds are determined using the mass flow rates, obtained from the velocity and porosity distributions in the bed. The mean residence time in the spout or annulus is an important parameter to calibrate granulation models that separate the fluidized bed in a wetting and drying zone (2-zone-models). At present, investigations are conducted under dry conditions and different liquid injection rates. The influence on the porosity and velocity distribution and on the residence time will be analyzed and discussed.



(a) (b)

Figure 1: Image of a spout fluidized bed with a jet velocity of $u_{jet} = 16u_{mf}$ and a fluidization velocity of $u_f = 2.3u_{mf}$ (a) and the corresponding velocity vector fields (b) in a pseudo 2-dimensional experimental setup with the geometry 300 x 1000 x 20

mm³ (W x H x D) using γ-alumina oxide as particle system with a particle size of d_p = 2.5 mm and density ρ_p = 1040 kg/m³

[1] Link, J., 2007: Development and validation of a discrete particle model of a spout-fluid bed granulator, PhD thesis, University of Twente, The Netherlands

Fiber-optical inline measurements of particle size distributions in fluidized bed processes

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In recent years a considerable progress in fibre-optic technologies has facilitated the development of small integrated inline particle analysis devices, used in a wide range of industrial applications for process-monitoring. An inline measurement probe (IPP-70S / Parsum GmbH) for the detection of the particle size distribution (PSD) and the velocity size distribution (VSD) in disperse particle systems, involving the principle of transmission fluctuation spectroscopy (TFS), was mounted into top-spray fluidized bed agglomeration units to study the dynamically evolving particle size distribution at various process parameters. To validate the inline measurement, comparative samples were periodically withdrawn and surveyed in a digital image analyzer (Camsizer). Due to the trajectory-independent measurement the Camsizer was considered to reflect the exact particle size distribution.

As the objective of the investigations was to adjust the inline measurement results to the offline data, the internal device parameters were adapted corresponding to the encountered state of fluidization. Further investigations have been conducted to determine the influence of the angular alignment of the probe inside of the fluidized bed, whereas the vertical measurement position remained unchanged. In order to describe the influence of particle concentration on the quality of measurements the bed mass was altered up to dysfunction of the probe.

Experiments with variation of bed mass indicated that measurement is not possible at volume concentrations larger than 30%, using particles of d_{32} = 180 µm. Ongoing investigations aim to develop a predictive concept, comprising the relation of bed mass, gas velocity and particle size (fluidization regime) to the functionality of the probe. The alteration of probe orientation did not suggest any impact on the quality. As a consequence of the vigorous particle growth dynamics in agglomeration processes, the d_{32} of the recorded PSD showed a parameter-consistent negative minimum deviation of 30%. This bias was associated to the presence of smaller particles in the measurement volume of the probe. As a solution, the raw data will be retrieved via an IP-interface, which afterwards will be implemented into an adjustment model. Furthermore, the probe shall be integrated in a control cycle, allowing an almost instantaneous reaction time for the regulation of particle growth rate.

Influence of the process parameters on particle properties during fluidized bed granulation

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The fluidized bed technology offers a variety of opportunities for applications in the field of drying and particle formulation. A special application is the fluidized bed spray granulation. Solutions, suspensions and melts as well as fine disperse particles can be converted into coarser and almost spherical particles and thus exhibit new properties. The particle structure is of significant importance, which influences the mechanical strength and thus the breakage and attrition resistance during the processing and the transport.

In this contribution experimental results regarding detailed analysis of the breakage kinetics of granules in dependency of process parameters are presented, whereby concentrations of the binder in the spray solution, particle retention time, different nozzle configurations and process temperature have been varied for two different materials.

The results show that the binder content in the injected solution has an important influence on the mechanical properties of granules. Furthermore, the spraying gas pressure of a two component nozzle showed a significant influence on the particle size distribution of the products, the number of agglomerates and the dust formation during the process. The process temperature has a minor influence on the mechanical properties of the granules and furthermore on the amount of dust formation during granulation.

Micromechanics of fine particle adhesion: contact models and energy absorption

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Dry, fine, cohesive and compressible powders (particle diameter d < 100 µm) show a wide variety of flow problems that cause insufficient apparatus and system reliability of processing plants. These problems include undesired adhesion or sticking at particle processing, and desired, at particle agglomeration, formulation or coating. Thus, the understanding of particle adhesion is very essential to assess the product quality and to improve the process performance in processing and technology of powders and agglomerates.

Comprehensive models are shown that describe the elastic-plastic force-displacement and frictional moment-angle behaviour of adhesive contacts of isotropic smooth spheres. By the model *stiff particles* with *soft contacts*, a sphere-sphere interaction of van der Waals forces without any contact deformation describes the *stiff* attractive term. But, the *soft* micro-contact response generates a flattened contact, i.e. plate-plate interaction, and increasing adhesion. These increasing adhesion forces between particles directly depend on this *frozen* irreversible contact deformation. This load dependent adhesion force contributes to the tangential forces in an elastic-plastic frictional contact. Considering all spatial degrees of freedom, the load dependent rolling resistance and torque of mobilized frictional contact rotation are also shown. Their consequences are discussed with respect to energy absorption. The total energy absorption comprises contributions by elastic-dissipative hysteresis due to microslip within the contact plane and by fully developed friction work. With increasing contact flattening by normal load, these friction limits, hysteresis and friction work increase.

Finally, conclusions are drawn concerning particle stressing, powder handling behaviour and product quality assessment in processing industries.

Modeling of agglomerate growth in fluidized bed spray drying

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Fluidized bed spray agglomeration is widely used as industrial process to enlarge particle size, improve powder flowability and, in general, to generate products with specific desired characteristics. The main principle of the process is the combination of distribution, particle reshaping and drying of a liquid feed upon a powder fluidized bed in a single apparatus promoting in this way the formation of bonds among single particles to generate conglomerates [1].

In the present work, the solid phase is represented by a population of non-deformable, non-porous, monosized and spherical particles. Agglomerate formation is considered as a complex network of consecutive and parallel micro mechanisms such as droplet capture and deposition on particles, droplet drying, particle collisions, liquid bridge formation with subsequent drying to produce solid bridges, and agglomerate breakage [2]. These micro mechanisms are modelled separately and implemented in a comprehensive model that is numerically solved by a stochastic method, namely the constant volume Monte Carlo method. This methodology allows the simulation of a finite representative sample of particle population during the course of the process.

Experiments varying several process parameters were carried out in an attempt to provide the data necessary to explain the influence of process conditions not only on the size enlargement as a whole, but also on each of the micro mechanisms.

The simulation results show that rate of the agglomeration process is directly proportional to the quantity of binder introduced to the system and thus to the droplet capture rate. However, no effect of the liquid flow rate is observed on the maximum attainable agglomerate size. The latter is influenced mainly by the equilibrium reached between particle coalescence and agglomerate breakage. This equilibrium is found to be very sensitive to variations of binder properties such as the size of the sprayed droplet. It was observed that small droplets lead to higher initial aggregation rates due to a higher droplet capture, whereas larger droplets allow to reach higher agglomerate diameters due to a higher absorption of the agglomerate collision energy (Fig.1).

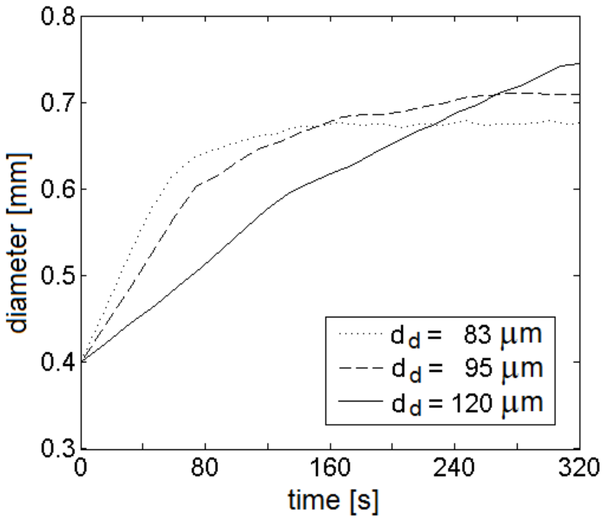

Fig.1. Effect of the droplet size on agglomerate growth

In conclusion, the model shows a promising way to simulate the formation and growth of agglomerates since it shows expected response to the variation of process conditions and follows the general experimental tendencies, not only regarding agglomerate diameter but also concerning the shape of particle size distribution.

[1] J. Drechsler, M. Peglow et al. Chem. Eng. Sci. 60 (2005) 3817-3833

[2] H. S. Tan, A.D. Salman et al. Chem. Eng. Sci. 61 (2006) 1585-1601

Particle-gas mass transfer in a spouted bed with controllable air inlet

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Fluidization with hot air is an attractive technology for processing and drying various kinds of moist powders and granular products. A wide range of applications requires reliable design models, based on fundamental knowledge of process kinetics and controlling steps. Spouted fluidized beds are a special apparatus configuration for producing high-quality products with reduced energy consumption in a single reaction chamber. Today, modern designs of spouted beds use two turnable shafts to create an air inlet opening of controllable width instead of a fixed inlet gap in the conventional modus. However, only a few studies about the pressure drop and flow, and no measurements of mass transfer, exist in literature for such modern spouted beds.

The present paper reports a systematic investigation of particle-gas mass transfer in a spouted bed with controllable air inlet regarding the determination of mass transfer coefficients. In the experiments α-Al_2O_3 was used as a porous carrier material. Moisturization was conducted with pure water. During the drying process the outlet gas moisture content was measured at various air inlet volume rates, velocities, temperatures and solid hold ups. By means of the moisture content of inlet and outlet air, during the first drying period, mass transfer coefficients between particle surface and fluidization gas were calculated. This observation was based on assumption of either perfect back mixing or of ideal plug flow of the gas. The coefficients were expressed as dimensionless Sherwood numbers. By using other relevant dimensionless numbers, a correlation for the spouted bed with controllable air inlet was developed. Furthermore, a comparison was conducted between Sherwood numbers for the investigated spouted bed, for conventional fluidized beds, and for conventional spouted beds in order to estimate the advantages and disadvantages of the new design.

Study of fluidised bed spray agglomeration focussing on the moisture content of the solids: I. The kinetics of fluidized bed spray agglomeration

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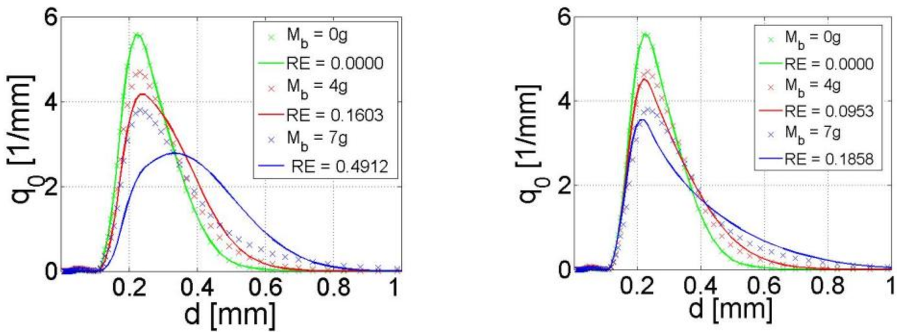
By agglomeration fine sized primary particles are transformed into free-flowing dustless consumer products. In case of an agglomeration process a number of primary particles adhere due to collision and the presence of a certain binder liquid which is brought into contact with the particles.
Population balance equation (PBE) describes the temporal change of number density with respect to a selected particle property. Frequently, the particle size or volume has been considered as the only significant property of the disperse phase. Thus, a one-dimensional population balance equation (PBE) for growth, agglomeration and breakage has been applied to numerous processes in chemical and pharmaceutical industry.

According to Watano [1] the moisture of the solid phase is a significant property, which needs to be taken into account to gain a better understanding of the kinetics of the agglomeration process. In the framework of this study the influence of mean particle moisture content on the kinetics of particle formation was investigated. The objective was to gain reliable experimental data in terms of evolution of particle size distribution and moisture content of particles during the agglomeration process. The data should allow to identify clear dependencies of agglomeration results on the process parameters and to extract kinetic data.

Therefore experiments were carried out in a batch fluidized bed. As test materials highly porous and non-porous primary particles were used. For a wide range the influence of different process parameters such as gas inlet temperature, mass flow rate of gas or spraying rate was investigated. The experimental setup enables the to determine the mean moisture content of the solids in-situ. Additionally, samples of the agglomerates can be discharged in constant time intervals to measure the evolution of the particle size distribution.

Kinetic data was extracted from the experimental results. Then the one-dimensional population balance was applied with two different types of kernels (EKE-kernel of Hounslow [2] and shear-kernel of Smoluchowski [3]). By solving the inverse problem [4] the pre-factor of the agglomeration kernel was determined. To prove the validity of the size dependent kernels the experimental results were compared with the PBE. It was found that the shear-kernel gives the best fit, while the EKE-kernel fails to predict the evolution of PSD, see Figure 1.



EKE – Kernel Shear-kernel

Figure 1: Simulated and experimental data of the size distribution for an experiment with γ-Al_2O_3 particles using the EKE-kernel and the shear-kernel at different binder contents M_b. The regression coefficient RE illustrates the deviation between simulation and experiment. The process parameters are: $\dot{M}_g = 70 kg/h$; $\vartheta_{g,in} = 40°C$; $c_b = 6 wt.-\%$; $\dot{V}_{n,l} = 1000 ml/h$.

In the framework of this contribution experimental and simulated results will be presented. Moreover the influence of the mean moisture content on the agglomeration kinetics will be discussed by means of population balance modelling.

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Study of fluidized bed spray agglomeration focussing on the moisture content of the solid: II. The size-distributed particle moisture content

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Fluid bed technology is of growing importance for a wide range of powder processing industries. In order to combine the benefits of simultaneous size enlargement and drying in a single apparatus, one needs to understand the fundamentals of the process. Thus, the experimental effort for the development of new material systems can be decreased, existing processes can be optimized.

In literature, approaches for the mathematical description of the process of fluid bed agglomeration often focus on macroscopic methods like population balance modelling. Population balances describe the dynamic change of the density distribution of a particle population. In the past, particle size d often was the only internal coordinate to be included in these one-dimensional models, even though Watano et. al. (1996) already found that the particle moisture content X influences the agglomeration kinetics significantly. Thus, in a first step Hampel et. al. (2007) investigated the impact of the mean moisture content of the solids on growth kinetics, expressed by the agglomeration kernel $\beta^* = f(\bar{X}, d)$.

The objective of the present study is to gain some knowledge experimentally about the moisture content of particle size fractions produced in a fluid bed agglomeration process. Therefore a novel sieving device for quick and non-destructive classification of agglomerates was constructed. After agglomeration in a lab-scale granulator, particles were discharged and fed into the device. Separated samples were analysed in regard of their moisture content by gravimetric measurement. The size distribution was determined by optical measurement. As a model system hygroscopic γ-aluminium oxide with a narrow size distribution was used. The primary particles were agglomerated by spraying hydroxyl-propyl-methyl-cellulose (HPMC). Binder concentration and spray rate were changed in two stages to create different degrees of wetting in the powder bed. In order to validate the experimental method an artificial moisture distribution within a particle population of different sizes was created and classified with the sieving device. Samples were taken and compared before and after classification to test the reproducibility of a size-dependent moisture distribution. Results of this study will be presented and discussed in the workshop contribution.

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The restitution coefficient of three types of wet granules

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During the processing and the transportation granules are stressed especially in fluidized beds and at pneumatic transportation. These granules contain different moisture contents. As a consequence of wetting and drying the mechanical properties of granules can be changed. To model and simulate the dynamics of granules in processing apparatuses the coefficient of restitution has to be known.

The normal and tangential restitution coefficient of different spherical granules has been experimentally studied. Free fall tests and canon shot tests have been carried out against a hardened steel plate to obtain the normal restitution coefficient that characterizes the energy losses during loading and unloading. The elastic-plastic γ-Al_2O_3, zeolite 4A and the dominant plastic sodium benzoate were selected as model granules. The particle impact velocities of the free fall experiments have been obtained between 0.5 – 4.5m/s. An inductor canon has been constructed for higher particle impact velocities that are in the range of 3.0 – 6.5m/s. The moisture content has been varied so that the pore saturation changed in the range of 0 – 1. A digital high speed camera was used to record the impact and rebound events. The camera has a frequency of 8.000fps. The tangential restitution coefficient has been examined by free fall tests. Different mechanic models for the restitution coefficient have been used to approximate the obtained results. The constitutive mechanical parameters like modulus of elasticity and yield velocity have been obtained by preliminary compression tests. The models fit well the measured data.

Breakage behaviour of agglomerates and crystal aggregates by static loading and impact

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Cylindrical agglomerates, e.g. tablets and briquettes, are important products of the chemical and pharmaceutical industry. During the processing sequence and transportation agglomerates are often subjected to repeat mechanical stressing that can lead to their breakage reducing product quality. An adequate description of agglomerate micro properties is required to improve the physical understanding of these macroscopic breakage phenomena. The general aim of this study is to combine the micromechanical properties of primary particles as well as the binding agent with the macroscopic deformation and breakage behaviour of dry agglomerates during mechanical stressing.

In this contribution the breakage behaviour of cylindrical □-Al_2O_3 agglomerates was studied. Compression tests of model agglomerates were performed. The effects of agglomerate size and binder content (hydroxypropyl methylcellulose) in dry agglomerates on their force-displacement and breakage behaviour were investigated. The modulus of elasticity, stiffness, yield pressure and strength of both, the agglomerate and primary particles, have been measured. The elastic compression behaviour was described by application of contact mechanics. The elastic stiffness of agglomerate increases linearly with the height of the cylinder. To approximate the ideally plastic force-displacement behaviour beyond the yield point, a simple contact model was developed. Increasing binder content yields an increase of the elastic and plastic stiffness, the yield and breakage limits as well as modulus of elasticity.

The second part of this contribution includes the study of breakage behaviour of (S)-mandelic acid crystal aggregates during impact. These investigations aim at describing breakage phenomena of crystal aggregates to derive the breakage kernel in a population balance model of crystallization. A new electromagnetic particle gun was constructed to perform collision experiments of single crystals with a wall at different velocities and impact angles. The main advantage of the developed device is the high adjustability and reproducibility of the particle impact velocity by voltage or current control.

To analyze the micro dynamics and breakage mechanisms for the experimentally investigated □-Al_2O_3 agglomerates and crystal aggregates discrete element models are proposed. The deformation and breakage behaviour obtained by experiments is used for calibration of model parameters. A good agreement between simulations and tests has been achieved.

SolidSim-Dynamics – A novel software for the dynamic flowsheet simulation of solids processes

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Nowadays, software tools for the flowsheet simulation of industrial processes are commonly used for design, simulation, balancing, troubleshooting and optimization purposes. Most of the tools are applicable to fluid processes only and cannot be effectively applied to processes which involve solids. One special program which was developed for the steady-state flowsheet simulation of solids processes is the program system SolidSim.

In this contribution we want to present the conceptual design of a new program applicable for the dynamic flowsheet simulation of complex solids processes 'SolidSim-Dynamics' which will be developed as enhancement of the steady state version of SolidSim. A hybrid simulation approach a combination between modular and simultaneous (equation-based) methods will be used as the basic simulation concept. Therefore, 'SolidSim-Dynamics' can use the benefits of both: better convergence rate of simultaneous approaches on the one hand and a bigger flexibility in creating flowsheets, the possibility of simultaneous usage of different solvers as well as effectively parallelization to the cluster of standard computers on the other hand.

The waveform relaxation method and its modifications are the basis for the modular dynamic simulation. The main idea of this method is that for a certain time interval different models can be calculated independently from each other while a solution for the simulation will be found iteratively.

As an example the flowsheet simulation of a series of connected fluidized bed granulators with complex milling, sieving, mixing and recycle streams will be discussed to show the application of the proposed simulation approach. The integrated unit operations like fluidization, drying, granulation and milling are using models of different complexity with regard to the physical mechanisms. The heat, mass, and

momentum transfer phenomena in terms of reaction-diffusion equations are coupled with a population balance of the whole particle ensemble, characterized by a partial Integro-differential equation. This allows the calculation of the time-dependent distribution of the particle size as well as temperatures and mass flows progressions (e.g.) in the granulators at different positions in the complex process chain.
The novel software is able to simulate the unsteady start-up behaviour of processes. The transient behaviour during the change of process or material parameters can also be examined. In the example case strong nonlinearities in form of damped or constant oscillations can occur.

Effect of the liquid layer on the impact behaviour of particles

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During a spray granulation process the moisture loading in fluidized beds has a great influence on the inter-particle collision properties and hence on the flow behaviour. The previous performed experiments showed that the main contribution to the energy absorption during the collision is made due to the shear flow of the liquid between collided granules with further formation, extension and rupture of the liquid bridge.

To study the influence of the liquid layer as well as granule impact velocity free-fall experiments were performed. During these experiments the γ-Al_2O_3 granules were dropped from a predefined height onto the liquid film on the target (flat steel wall) and the velocity-time curves obtained due to high-speed video recording of granules captured close to the contact point. The height of the liquid layer was varied from 25 µm to 1mm. Moreover, the impact velocities from 1 m/s to 2.3 m/s, the impact angle from 0° to 80° and the viscosity of liquid film in the range of 1-50 mPa·s were varied. Both distilled water and the water solutions of hydroxypropylmethylcellulose (Pharmacoat® 606) with different concentrations (3, 6, 10 mass-%) for variation of viscosity were used.

The obtained restitution coefficients were compared with the experiments performed with dry γ-Al_2O_3 granules without liquid film on the surface. For a granule impacted on a liquid film on the wall, the increase of liquid viscosity decreases the restitution coefficient and thickness of liquid layer at which the granule sticks. In the examined velocity range, with decreasing impact velocity the restitution coefficient greatly decreases. To explain the obtained effects the force and energy balances for a particle impacted on a liquid layer on the wall were derived. Both contributions to energy absorption (granule-liquid layer and granule-wall contacts) have been taken into consideration.

Analysis of the fluidization behaviour and application of a novel spouted bed apparatus for spray granulation and coating

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Recently the importance of the spouted bed technology has significantly increased in the context of drying processes as well as granulation, agglomeration or coating processes. Analogous to conventional fluidized beds, spouted beds are well known for their good mixing of the solid phase and also for their intensive heat and mass transfers between the fluid phase (gas) and the solid phase yielding nearly isothermal conditions. The special flow structure of a spouted bed is characterized by a gas jet in a strongly conical or prismatic process chamber.

The main difference of spouted beds in comparison with conventional fluidized beds is the variable cross section area of the apparatus as function of the apparatus height. Particulate systems concerning very fine or non-spherical particles that are difficult to fluidize, often cannot be treated in conventional fluidized beds. Contrary to those fluidized beds, the spouted bed technology with its specific flow structure offers the opportunity of stable fluidization under controlled conditions. The advantages of the new technology are most obvious in spray granulation processes when very fine particles of homogeneous structure and uniform surface must be produced. Further, coating processes involving the application of very high amounts of coating material can be carried out because fine and also much larger particles together can be fluidized more easily in this machine than with the conventional fluidizing process. The knowledge of the stable hydrodynamic operation range of the spouted bed, which is smaller compared with conventional fluidized beds, is of importance for operating the apparatus. The hydrodynamic operation ranges of spouted beds are usually characterized in a quantitative manner by analysis of gas phase pressure fluctuations.

The focus of this work is in the first part the investigation of the hydrodynamic behavior of a novel spouted bed apparatus with two horizontal and adjustable slit-shaped gas inlets. By measured gas phase pressure fluctuations and Fourier analysis on these spectra, the hydrodynamic stable operation range is identified and depicted in the dimensionless Re-G-Ar-diagram by Mitev (1979). The particle system, the gas throughput and the cross section area of the gas inlets are varied. With the results of this work, a comparison is made with stable operating ranges of other fluidized or spouted beds, which already have been characterized by several authors.

Furthermore, 2D-CFD continuum simulations of the hydrodynamics of the investigated prismatic spouted bed are carried out in the commercial software package FLUENT 6.2. Realistic values of the coefficient of restitution for the experimental material (monodisperse □-Al_2O_3-particles) are used. Moreover, the influence of different gas-particle drag models on the distribution of the granular solid phase in the apparatus are tested and compared with images taken during experiments. The calculated gas phase pressure fluctuations over the entire bed are compared with measurements. Also Fourier analysis on the measured and simulated pressure frequency spectra are contrasted.

Based on the novel spouted bed apparatus Glatt has developed the innovative ProCell - processing unit to carry out various processes like spray granulation, coating, agglomeration and heat transfer.

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 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 second part of the work is related to industrial examples of ProCell – applications.

An experimental study of the effect of collision properties on spout fluidized bed dynamics

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Spout fluidized beds are frequently used for the production of granules or particles through granulation, which are widely applied for example in the production of detergents, pharmaceuticals, food and fertilizers. Spout fluidized beds have a number of advantageous properties, such as high mobility of the particles preventing undesired agglomeration and enabling excellent heat transfer control. During the granulation process, the particles contain different loadings of moisture which results in varying collision properties in time and location across the bed. However, little is known about the effect of the collision properties on the bed dynamics, and thus on the granulation process. This is mainly due to the fact that it is not visually accessible. In previous conducted numerical studies the effect on the collision properties, i.e. the restitution coefficient, are investigated on the bed dynamics. In Figure 1 it is shown that if the restitution coefficient decreases, more bubbles are present causing more instability in the overall dynamics of the bed in more or less extent dependent on the flow regime. These conclusions show the great importance of the influence of the restitution coefficient on the dynamics of the bed. Therefore, an experimental study is of interest to examine different particle systems with different collision properties in a spout fluidized bed. In this work a non-intrusive measurement technique is used, *viz.* particle image velocimetry (PIV) to measure the particle flow field in a pseudo two-dimensional spout fluidized bed. Additionally, digital images are analyzed using a proposed digital image analysis algorithm (DIA) to evaluate the particle volume fraction. The experiments are conducted with different particle systems, such as glass beads, γ-alumina oxide and zeolite 4A particles. Each particle system is applied in three different flow regimes: intermediate/spout-fluidization regime (case B1), spouting-with-aeration regime (case B2) and jet-in-fluidized-bed regime (case B3). The experimental results of the different particle systems will be compared, taking the differences in density and particle size into account.

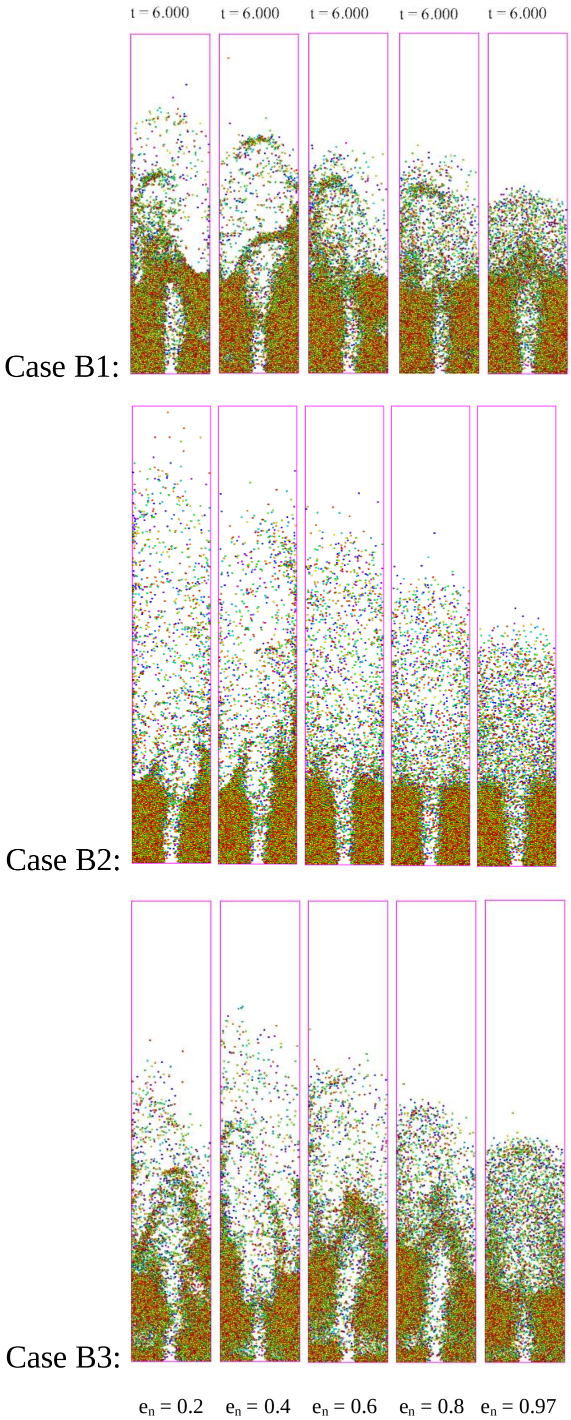

Figure 1: Snapshots of the simulated instantaneous particle positions for different restitution coefficients for case B1 (intermediate/spout-fluidization regime),

B2 (spouting-with-aeration regime) and B3 (jet-in-fluidized-bed regime) at simulation time t = 6.0 s (after M.S. van Buijtenen et al., ICMF 2007, Leipzig, Germany).

A comparison of fluidized hot melt granulation and conventional wet granulation using model water-soluble and poorly water-soluble API

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Fluidized hot melt granulation (FHMG) is a novel granulation technique to process pharmaceutical powders. The purpose of this work is to determine the feasibility of FHMG as a pharmaceutical granulation process and also to compare the advantages and disadvantages of FHMG with the conventional wet granulation using both a water-soluble or poorly water-soluble API.

Three granulation methods (a wet granulation and two FHMG processes), two model drugs and two drug loadings (2% & 20%) were compared in this study. A low-melting co-polymer of polyoxyethylene-polyoxypropylene (Poloxamer188) was used as a metable binder for granulation purposes in FHMG, whilst 5% PVP aqueous solution was used as a liquid binder for conventional wet granulation. In FHMG two granulation methods were used. Method 1 involved using polymer alone as the meltable binder, granulated with the physical mixture of fillers and API, which is referred to as 'FHMG PM' hereafter. Method 2 ('FHMG SD') involved pre-dissolving the drug into the meltable binder using a hot melt method. The solidified drug-polymer solid dispersions were consequently used as the meltable binder, and granulated with the mixture of fillers. Similar formulations were used in all granulation techniques. The bulk/tap densities, flowability of granules and the drug content in each size range were also evaluated. The granules were then pressed into tablets. The properties of tablets such as friability, hardness, uniformity of content and drug release profile were investigated and compared.

The granules produced by FHMG showed lower bulk/tap densities and better flowability than the granules produced by wet granulation. The drug content in different size range of granules produced by FHMG SD illustrated good uniformity in both water-soluble drug and poorly water-soluble formulations, while for the wet granulation process, the smaller particles contained more drug than the larger particles. The hardness of tablets produced by the granules from FHMG technique was lower than the tablets made by wet granulation process. The drug release rate of both water-soluble and poorly water-soluble API was increased by using the solid dispersion as a binder for FHMG.

FHMG is a simple and novel granulation technique, which is suitable to process both water soluble and poorly water soluble API. In Comparison to conventional wet granulation, FHMG avoids the use of liquid binder for agglomeration, has no drying step, and hence could save time and energy from the granulation process. The application of solid dispersions in the FHMG is an effective strategy to improve the drug content uniformity and the dissolution rate.

Relationship between particle shape and some process variables in high shear wet granulation using binders of different viscosity

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Controlling granule shape may be desirable for many reasons; among these are for example the flow properties. A spherical shape possesses a minimum surface area to volume ratio resulting in reduced cohesive forces and mechanical interlocking thereby resulting in a improved flowability of the bulk powder. Obtaining spheronisated shape is a desired prerequisite also when a subsequent coating or drug layering of the granules is necessary.

The advantage of wet granulation process in high shear mixer is that mixing, massing and granulation are performed in few minutes in the same equipment. However the high shear wet granulation (HSWG) process does not always warrant spheronisated granules. The process needs to be controlled with care as the granulation progresses so rapidly that a usable granule can be transformed very quickly into an unusable system.

The focus of this paper is therefore on the influence of process parameters on granule shape. Two different systems have been considered and results compared. Both systems include a fixed mixture of Microcrystalline Cellulose and Monohydrate Lactose as powder mass but two different binders were considered. In the first case water was considered whereas in the second case an oil-in-water emulsion was used as liquid binder in order to produce a solid self-emulsifying systems. All experiments were performed in the same vertical, bottom driven high shear granulator. The results obtained through DOE plus data statistical analysis showed that some of the process variables studied (impeller speed, granulation time, amount of initial powder and of binder) were able to induce different granule shapes. In particular a clear dependence on the binder quantity and on its nature has been observed and two main behaviours were individuated. Final structure of granules depended on structural changes which occurred during the granulation process and these were determined by the rheology of the wet bulk. Granules must be strong enough to resist the forces in the granulator, and deformable enough to generate spherical granules. Using an excess of liquid both binders produced a loss of roundness. Different surface characteristics were also observed. In particular using water, pellets resulted smaller, more rough ad with irregular shape. Composition of the second system containing an oil-in-water emulsion produced longer, more flat and smooth aggregates. These differences have been quantified using various shape factors and explained in terms of MCC granulation mechanisms where phenomena such as powder wettability, binder adsorption/desorption, intra- and inter-particle lubrication play a major role. Measures of granules strength were used in addition to corroborate our conclusions.

Analysis of low shear granulation and tabletting of pharmaceutical powders

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Low shear granulation, which is a form of wet granulation, is an important unit granulation in the pharmaceutical, detergent and food industries. The granulation mechanisms for wet granulation include wetting and nucleation, consolidation and growth and attrition and breakage. In an experimental study the influence of process parameters on the low shear granulation was investigated using lactose and starch as model powders and CMC solution as a model binder. Four parameters: binder viscosity; binder content; different ratio of starch to lactose and shear rate, were investigated at granulation times of 1 and 12 minutes. The data indicated that increased mass mean diameter and was found using higher viscosity binders, however increasing the impeller speed resulted in lower mass mean diameters suggesting that granule breakage has an important influence on this agglomeration process. The granulation data were successfully described by using multivariate statistical analysis. Moreover, three different size ranges of granules taken from the low shear granulation processes under various processing conditions were subsequently pressed into tablets using tablet press. Standard pharmaceutical hardness and disintegration analyses were performed on the tablets. These analyses indicated that the formulation (i.e, starch/lactose and liquid/solid ratios) rather than granulation process parameters had more influence on the mechanical properties of the tablets.

Studies on the physical properties of biodegradable films for detergent encapsulation

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Water vapour permeability through films is generally desirable in detergent powder/granule applications, whereby a film is used to encapsulate another medium and is needed to disperse in wet conditions; moreover a highly hydrophilic material can be advantageous in these processes. In this work, the films of four chosen materials (carboxymethyl cellulose (CMC), carrageenan, sodium alginate and gelatin) were investigated to compare the influence of thickness, clarity, tensile strength and water vapour permeability on the pre-set design constraints for detergent powder/granule applications. The influence of the addition of plasticizers (glycerol, poly (ethylene glycol – ran – propylene glycol), polyethylene glycol (PEG) 200 and 1, 2-Propanediol) was also examined. It was discovered that both CMC and sodium alginate provided the best films regarding overall strength and clarity with respect to thickness. Sodium alginate was discovered to be the most permeable to water vapour. However, CMC was revealed to be the toughest and most transparent of all the films and, although the permeability was slightly less than that of sodium alginate, it was revealed to be the optimum material of those investigated for detergent powder/granule applications.. The affect of the addition of plasticisers was also investigated and it was concluded that, although the plasticisers improved water solubility and permeability of the films, the clarity and tensile strength deteriorated significantly.

The phenomena of liquid marble formation using hydrophobic and super-hydrophobic powders

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This work aims to investigate and quantitatively measure "liquid marble" phenomena using hydrophobic and superhydrophobic powders (granules). 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. The hydrophobic powder poly-methyl methacralate (PMMA) particle size 42µm and contact angle of 120º was also used to determine the effect of powder density on liquid marble stability. The experimental investigations indicated that for successful formation of liquid marbles a number of variables in addition to hydrophobicity need to be considered, namely: powder density; powder particle size; powder shape; liquid marble formation technique. It was found that liquid marbles were formed using all four powders to varying extents, with a low powder particle size forming more stable liquid marbles. In a series of gravimetric tests, adhered powder mass on liquid marbles was found to be directly proportional to the water droplet surface area. A more complete coverage of the water drops were found with PMMA powder than the superhydrophobic materials. Furthermore, a procedure was developed to increase the mechanical strength of the liquid marble, by polymerising MMA on the surface of a PMMA powder - liquid marble, with the aim of maintaining water within a more robust PMMA - liquid marble shell. This technique may prove to be a novel way of encapsulating drug compounds, such as gentamicin sulphate, for use in PMMA bone cement applications.

Analysis of in-vitro drug dissolution from a PCL melt extrusion process

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This study investigated the in-vitro release of a model API (Nalidixic Acid) from a PCL bulk extrudate and determined how the extent and rate of drug release are affected by the addition of a pore former (PEG) and of a copolymer (PLLA) within the polymer matrix. Drug release and dissolution is a mass transport operation and therefore can rely on both molecular and bulk diffusion. Typical drug delivery systems are made up of three components; a matrix structure (which does not diffuse and hence, its diffusion coefficient is zero), solution (coming in from the external environment and moving inside the matrix structure) and drug (that usually diffuses from the inner matrix into the external release environment). The release from blends produced by both crash cooling and controlled cooling were considered, alongside those processed via both single and twin screw extrusion. From analysis of the extrusion process it was found that the polymer crystal size was smaller in blends prepared using a 100degC/min cooling rate than those prepared using a 30degC/min cooling rate. Furthermore, the solubility of NA in PCL was improved by a factor of 2 by increasing cooling rate which was attributed to higher percentage of amorphous regions. Moreover, a higher degree of NA release was observed in the faster cooling rate due to the increased solubility. The experimental kinetic drug release data were modelled using a number of simple approaches, and it was found that the Kosmeyer-Peppas model was best at describing the experimental data, with $r^2 \geq 0.993$. Finally, the hydrolytic degradation of the extrudates at 37°C (under static aqueous conditions over the period of six months) was also analysed to determine degradation rates.

Effect of nucleation mechanism on granule properties in fluidised hot melt granulation

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In this study Ballotini of standard size (125-250µm) were granulated with poloxamer of various particle sizes (45-90µm, 125-250µm; 710-1000µm), i.e, binder particle sizes that were, significantly smaller, approximately the same and significantly larger. The experimental data indicate that a higher mass mean diameter was achieved using higher initial binder particle size. For granulation using the lowest binder particle size, granule growth initially increases rapidly (i.e., non-inertial coalescence) but reached a maximum after a relatively short period of time and then decreases gradually for the rest of the experiment. For the largest binder size the data indicate some induction (due to heat transfer effects) followed by rapid growth by an immersion process when the binder melts and then slower growth which can be attributed to layering (i.e., Rebound Regime). The granules from the melt granulation study were subsequently analysed for in-vitro granule dissolution to determine if the granule nucleation and granulation mechanism would affect drug release within a pharmaceutical melt granulation context. Significantly, this was indeed found to be the case, whereby for "immersion" granules (i.e., granules formed from an immersion nucleation process) the dissolution time of the agglomerate in-vitro was three times longer than that of equivalent "distribution" granules (i.e., granules formed from a distribution nucleation process). For "immersion granules", it was observed that ballotini were being removed one layer after another, thus replicating the granule formation process in reverse.

Effects of the binder and filler properties on agglomerate growth during fluidized hot melt granulation (FHMG) process

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Fluidized hot melt granulation (FHMG) is a novel granulation technique for processing pharmaceutical powders. Various process variables are being investigated and several parameters have significant influence on granulation characteristics. Our study was performed in order to investigate the effects of the binder and filler properties such as binder particle size, binder viscosity, and the hydrophilic/hydrophobic properties of filler on the agglomerate growth mechanisms of fluidized hot melt granulation.

The low-melting point co-polymer of polyoxyethylene- polyoxypropylene (Lutrol® F68 Poloxamer188 and Lutrol® F127 Poloxamer407) were used as meltable binders for the FHMG, while the hydrophilic and hydrophobic ballotini beads were used as model fillers for this process.

The binder particle size, binder viscosity and hydrophilic/ hydrophobic properties of filler were found to affect the onset time of the effective granulation. Larger binder size and higher hydrophobic properties of the filler could prolong the start point of effective granulation. The agglomerate growth achieved equilibrium within short times. After the first effective fast agglomerate growth process, granulation equilibrated between the breakage of formed granules and the re-agglomeration of the fractured granules. The breakage properties were affected by the initial material properties. When using smaller binder size, agglomerate growth by distribution was found to dominate. Increasing the binder size increased the formation of agglomerates by an immersion mechanism. The critical ratio between the particle size of binder and filler could be a very useful parameter for predicting or controlling the granulation growth process.

Effect of high shear granulation parameters on the production of a granola cereal aggregate

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Granola is a cereal food product which can be used as a breakfast cereal or snack and is made of cereals, rice and honey. A high shear mixer granulator was used to produce granola in a wet granulation process (with honey mixed with some water as binder) followed by oven drying. The aim of this study was to investigate the effect of granulation parameters; impeller speed, binder addition rate and wet massing time on key granola physical properties. A laboratory scale 'Procept' 4M8 high shear granulator was used. A honey-water mixture (95:5) was used as the binder. Experiments were carried out at impeller speeds of 200, 300 and 400 rpm, binder flow rates of 0.216, 0.325 and 0.650 g/sec and wet massing periods of 6, 9 and 12 min. The granola was then dried on an oven at 160 ˚C for 10 minutes. Particle size distribution and granule strength were measured using a camsizer and texture analyser.

The agglomeration behaviour was found to vary greatly with impeller speed. Granules formed at low impeller speed were found to have low relative density. The experimentation allowed the optimal ranges of impeller speeds, the liquid binder flow rate, the wet massing time and torque to be established, therefore rendering the manufacturing process controllable and reproducible.

Markov chain modelling for fluidised bed granulation

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Fluidised bed granulation (FBG) is a particle size enlargement technique especially prevalent in industries concerned with pharmaceuticals, detergents, fertilisers, and food. Modelling of FBG is important in order to understand, control and optimise the process. Population balance modelling (PBM) is the most common tool to model such particulate systems and is quite powerful in analyzing the dynamics of the process. However, the structure of PBM is complex due to the intrinsic partial integro-differential equations and hence analytical solutions may not be possible except for simple cases. In this paper Markov chain simulation, which is one of the better known stochastic approaches, is introduced in order to model and analyse particle size enlargement in fluidised bed granulation where aggregation and breakage occur simultaneously. Such Markov modelling is based on mass balance equations as with population balance modelling (PBM). From this perspective, it can be viewed as a possible discrete solution mechanism of PBM. Moreover, it offers the possibility of replacing PBM in some aspects of granulation analysis, since it has equal efficiency but is less time consuming. In addition, the transformation of more then one property (in addition to size) of the particulate system can be simultaneously analysed.

A Markov process is defined by a transition matrix *P*, a state vector *a(t)*, and a transition time step, τ . The transition matrix *P* has entries p_{ij} which represents transition probabilities from state *i* to state *j* at each time step. The *P* matrix is built up by using the breakage frequency, aggregation frequency, breakage kernel, and aggregation kernel which come from population balance modelling terminology. Particle size is quantified using mass and is discretized into 100 states; the time step is 1 s.

For this study, the size enlargement process of glass beads is examined. These consist of spherical particles whose diameter can be represented by the Normal distribution with μ = 0.250 mm and σ = 0.014 mm. 10 g PEG (Poly Ethylene Glycol) with 60% concentration is used as the binder for a 200 g batch. The results show that Markov chains are an efficient tool to model the granulation process. Particle size enlargement and the shape of particle size distributions during the granulation process have been estimated within acceptable errors.

Modelling of particle motion in a recirculatory fluidised bed; prediction of process residence times

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Fluidized bed technology is commonly used in the pharmaceutical industry for the production of granules. One common arrangement is where a systematic circulatory motion is superimposed on the random fluid bed motion of the granules by controlling the air flow pattern in the system. The fluidized granules travel up an inner tube (known as a riser), exit out the top into the main chamber, fall down the annular space between the tube and the chamber and then repeat the motion. A liquid binder is sprayed over the granules as they pass through the inner tube to promote agglomeration.

One fundamental property of the granules is their velocity and consequent displacement versus time history. Velocity informs most of the sub-processes of granulation including the probability of contact with liquid binder droplets, the drying rate of the wet film on the granules, the collision probability with other particles or granules and the probability of subsequent coalescence (through the Stokes Number). Furthermore knowledge of velocity enables two important temporal process parameters to be quantified; these are the circulation time of the motion (time to complete one full pass through the system) and the residence time of the particles in the spray zone. Both these process durations strongly influence the outcome of the granule growth process and in turn can have a marked dependency on instantaneous granule size.

This paper describes the development of a model of granule motion incorporating the forces of weight and a turbulent air drag. The model provides a theoretical description of the motion (displacement and velocity) of the granules, its sensitivity to particle size and hence the magnitudes of the circulation time and spray zone residence time. Spherical and non-spherical granules are considered. The predictions of the theoretical approach are validated against numerical solutions of the governing differential equations of motion and against experimentally recorded displacement versus time histories of the particle. The validated output is used to characterize the system in terms of residence times for different granule size classes.

Population balance modeling of granola breakage during pneumatic conveying systems

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Granola is an aggregated food product which serves as a breakfast cereal or snack consisting of oats, cereals, rice and honey. Particle breakage of aggregated granola can occur during pneumatic conveying as product is transferred as part of the production process on its way to packaging. Such breakage occurs as a result of particle-particle and particle-wall collisions. In this work, a population balance model is developed for the breakage of granola that is conveyed through a pneumatic conveying pipeline rig. The model includes the influence of conveying pressure, exposure time and pipeline geometry, and is also related to parameters associated with aggregate formation such as granulator mixing speed and time. The aggregates were formed in a high shear mixer subject to impeller agitation at 300 rpm for 9 minutes and were then propelled through a pipeline with a 90^{o} bend at a number of different flow rates. Trials were carried out by applying compressed air at pressures of 100 kPa, 300 kPa and 500 kPa and over a number of recycles. Modelling of this breakage process was achieved by constructing the population balance equations (PBEs) in the form of a mass balance on particles of granola. The solution of PBEs were carried out by means of a discretization through the application of the Markov chains method. When the size range of the system was divided into a reasonable number of states, the Markov cahins method for the population balances exhibited a good approximation for predicting the particle size distribution (PSD) over time during the breakage of the granola aggregates.

Relationship between mechanical properties and shape descriptors of wet granules

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Fluidized bed technology is employed to achieve granulation of particles with the net agglomeration process being defined by the nature of the inter-particle collisions. Either size enlargement or alternatively attrition and breakage can result from these collisions. In addition, collisions between granules and the walls of the equipment have a significant effect on the evolution of granule size. To understand and predict the outcome of such collisions, knowledge of the mechanical properties of the granular material is required. This paper focuses on two such properties, the coefficient of restitution and the granule strength. In particular, this work examines their sensitivity to geometric parameters of the granules.

The system under analysis consists of the Würster granulation process based on fluidized bed bottom-spray granulation. The fluidized granules travel up an inner tube exit out the top into the main chamber, fall down the annular space between the tube and the chamber and then repeat the motion. The granules were assembled from 268 μm mean diameter glass beads with an aqueous solution of PEG1500 as binder.

The coefficient of restitution was measured for both the individual glass particles and for the granules. Collisions were arranged between granules and for granules against a flat glass plate. Both dry and wet collisions were examined; the latter obtained by covering the sheet glass with a thin film (< 0.5 mm thickness) of PEG1500. Using image analysis techniques (an X-Motion Pro high speed camera with ProAnalyst dynamic displacement analysis software) the ratio of the velocities of the granules before and after the impact was determined. A texture analyzer (TA-HD Plus, Stable Micro Systems) was used to measure granule strength.

Granule shape was quantitatively described using the parameters of sphericity, lacunarity (Λ) and fractal dimension (D_F) of the granule projected area. The D_F gives an indication about shape regularity while Λ indicates the homogeneity in the distribution of the empty spaces inside granule structure, as a complementary measurement for porosity, which was also determined. Granule size (diameter) was maintained at close to 1 mm for all tests.

Mean granule strength found was quantified as 1.13 N with the strongest granules returning values close to 1.4 N. Results demonstrated that granules giving the highest values for strength have the largest fractal dimension (D_F = 1.68) and the smallest lacunarity (Λ = 0.33) values regardless of their sphericity. The coefficient of restitution of the individual glass particles stabilizes around a value of 0.64 for dry impact on the flat glass and the 0.5 for wet impact. For the granules this parameter is close to 0.44 for both situations and between them.

One possible explanation for the measured granule strength versus shape relationship could be that the more irregular the shape (the larger the D_F) and the more homogeneity in the distribution of empty spaces inside the granule (i.e. the smaller the Λ) the greater the scope for dissipation of energy which allows the granules be more resistant against breakage.

A comparative study of powder compression behaviour during roller compaction and uniaxial compaction

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Although direct compression is the most favorable manufacturing process for the production of tablets in the pharmaceutical industry, it may not be feasible to utilize the process due to potential segregation, poor material flow and processing properties of these formulations (i.e. effects related to particle size distribution, compressibility, packing properties and cohesive nature of powders).

To improve the flowability and processing properties, granulation is hence required prior to tableting. There are two main types of granulation process : 1) wet granulation and 2) dry granulation (roll compaction and slugging). One of the distinctive advantages of roll compaction over wet granulation is that no moisture and negligible heat are involved in the process so that it can be used to process moisture, solvent or heat sensitive formulations. During the continuous roll compaction process, powders are compressed into strips (also called ribbons) or fragments of compacted materials that are then milled to produce granules. Due to the complex nature of processing conditions and diversity of formulations used in pharmaceutical industry, the fundamental mechanisms of roll compaction are not well understood. Historically, systematic studies into roll compaction have been conducted [1, 2], however an in-depth validation of the data and modeling efforts is still lacking [3].

In this paper a systematic investigation on roll compaction of microcrystalline cellulose (MCC, Avicel PH102) is presented. The MCC powder is roll compacted using an instrumented roll press developed at the University of Birmingham. The compression behaviour during roll compaction is investigated by systematically varying the processing parameters (i.e. roll gap and roll speed). Pressure-displacement relationships are obtained from the experimental data and are interpreted using the Kawakita equation. Furthermore, corresponding uniaxial compaction studies are also performed. A comparison of the compression behaviour during roll compaction and uniaxial compression are made to explore how the powder behaves during these two different compaction processes. The unloading behaviour of uniaxial compaction and roll compaction has also been analysed. The objective of the study is to assess if characterization of the compression behaviour of MCC using uniaxial compaction can be used to evaluate its behaviour during roll compaction.

It has been shown that, based on the analysis using Kawakita equation, the compression behaviour of MCC during these two compaction processes are similar when the roll speed is low. At high roll velocities different compression behaviour is observed. Furthermore, at higher porosity the Kawakita relationship shows deviation from lower porosity fits for ribbon compacts produced at different roll gap settings. It has also been found that ribbons produced using roll compaction tend to have a similar relative density to tablets produced at the same final thickness and maximum pressures using uniaxial compaction.

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Roller compaction of moist powders

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Roller compaction is a dry granulation process for producing large granules with fine powders in order to improve the flowability and homogeneity of pharmaceutical formulations. The compression behaviour of powders during roller compaction is dominated by a number of factors, such as process conditions (roll speed, roll gap, feeding mechanisms and feeding speed) and powder properties (particle size, shape, moisture content). The moisture content affects the powder properties, such as the flowability and cohesion. It is still not clear how the moisture content will influence the powder compression behaviour during roller compaction.

In this study, the effect of moisture contents on roller compaction behaviour of microcrystalline cellulose (MCC, Avecel PH102) was investigated experimentally. MCC samples of different moisture contents were prepared by mixing as-received MCC powder with different amount of water that was sprayed onto the powder bed agitated in a rotary mixer. The flowability of these samples were evaluated in terms of the poured angle of repose and flow functions that were determined using a ring shear cell. The moist powders were then compacted using the instrumented roller compactor developed at the University of Birmingham. The roller compactions were performed at roll speeds of 1rpm and 2 rpm with a roll gap of 1mm. The flow and compression behaviour during roller compaction and the properties of produced ribbons were examined.

It has been found that the flowability of moist MCC powders decreases as the moisture content increases and the powder becomes more cohesive when the moisture content increases. The drag angle that was proposed to characterize the uniformity of powder feeding into the compaction region slightly increases with the moisture contents increases. All produced ribbons have a higher density in the middle and lower densities at the edges. Different hydration states were also indentified from SEM images. Moreover, it was interesting to find that the ribbons made from the powders with higher moisture contents were split into two halves. This is attributed to the reduction in the mechanical strength of moist powder compacts with high moisture contents produced at high compression pressures.

Numerical analysis of density-induced segregation during die filling in air

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In this study, the segregation behaviour of binary powder mixtures with the same particle size but different densities during die filling in the presence of air was investigated numerically using a combined discrete element method (DEM) and computational fluid dynamics (CFD) approach, in which the particles were modelled using DEM, the air was analysed using CFD and a two-way coupling of the particles and the air was incorporated. Die fillings from stationary and moving shoes into the dies with different sizes were simulated and the corresponding segregation behaviours were analysed. To quantify the degree of segregation, a segregation index was introduced and defined as the volume weighted root mean square deviation of the concentration of light particles..

It has been found that, after the die filling from a stationary shoe, the concentration distributions of the heavy and light particles along the die width mainly depend on the initial packing of the granular mixture in the shoe. However, the density difference causes segregation in the vertical direction with a low concentration of light particles at the bottom. The presence of air increases the degree of segregation by resisting the flow of the light particles into the die, thereby creating a higher depletion of light particles at the bottom and an excess of light particles at the top.

During die filling from a moving shoe, segregation with a lower concentration of light particles on the leading side of the die is induced for die filling with a square die. This is attributed to the predominant nose flow that occurs during the die-filling process. In the vertical direction, segregation is also caused by the density difference with a depletion of light particles at the bottom of the die. If air is present, the degree of the segregation is increased and an excess of light particles migrate to the top of the die.

It has also been shown that, when the die filling process is dominated with the flow of particles from the bottom of the powder bed and when air is not present during the process, the segregation index becomes smaller, indicating that a lower degree of segregation is induced.

The influence of viscoelasticity on interparticle adhesion

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Wet granulation involves the addition of a liquid binder to the feed powder. The binder is usually in the form of a solution or a melt and the granules are stabilised by drying or cooling. It is well established that the capillary and viscous forces are responsible for the cohesion of the granules in the wet state. However, the role of viscoelasticity in the case of polymeric binders is often ignored. Moreover, complex fluids may exhibit flow anomalies at small solid-solid separations that can arise from (a) the relative importance of the solid-liquid interfacial interactions and/or (b) flow confinement when the structural length scale of the liquid becomes of the order of the separation distance.

The current work involves an experimental study of the interparticle adhesive properties of a viscoelastic liquid when confined to small dimensions. A range of film thicknesses and liquid viscosities have been investigated. The interparticle forces and the critical conditions leading to particle-particle separation were examined using colloid probe atomic force microscopy over a range of velocities. The results show that the film thickness and interparticle velocity are key parameters in determining the effectiveness of thin films as binders. In order to obtain a detailed understanding of the data, a theoretical model was developed that incorporates the viscoelastic properties of the binder.

Impact of solid properties on flow structure and particle motions in bubbling fluidisation

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Knowledge of solid motions and flow structures in fluidised beds is of significant importance to a number of industrial processes, such as combustion, gasification of solid fuels, drying of particulate materials, oxidation or reduction of ores, catalytic and thermal cracking. Through PEPT studies, we found that the flow structure and solids motion in a fluidized bed vary significantly with solid properties such as the solid density and particle size. Three flow structures have been found. For solids with a high density and a large size (>700μm), a single large circulation cell is observed within the whole bed, and particles move upwards at one side of the bed to the splash zone, and then return to the bed bottom along the opposite side of the bed. When the particle size is in the range 200-400 μm, particles move upwards across the whole area of the bed at relatively uniform velocity in a layer 30 mm deep immediately above the air distributor. Above this layer, solids move inwards and travel upwards in the centre of the bed to the splash zone, and then return to the bottom of the bed in an outer annulus. When the particle density is low or the particle size is in the range 50-100 μm, the fluidized bed can be divided into three sections. In the bottom section, solids travel upwards in the outer annulus, and move down in the bed centre. In the top section, solids travel upwards at the centre of the bed to the splash zone and then return to the intermediate height of the bed via the outer annulus. In the intermediate section of the bed (60-100 mm above the distributor), the annular upward solid flow from the bottom section encounters the annular downward flow from the top section. The two solid flows merge and change direction towards the bed centre where the particles are mixed and redistributed to the circulation cells in the upper and lower sections.

Effect of liquid binder on solids flow pattern in a conical high shear mixer

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The main mechanisms involved in wet granulation are known to be wetting and nucleation, consolidation and growth, breakage and attrition. All of them are related to the relative motion of particles in a granulator. During granulation processes, the driving force in a high shear mixer is introduced by the agitation blades, and then transmitted by particle collisions and liquid bridges. The surface tension and viscosity are therefore important properties of the liquid binders. They could be used to control the solids flow pattern and relative motion of particles for further controlling the wetting, granule growth, consolidation and breakage.

In this study, experiments are designed to investigate the impact of the surface tension and viscosity of liquid binders on the solids flow pattern and the relative motion of particles in a high shear mixer granulator. PEPT is used to track the solid motion. Hollow glass ballotini with an average diameter of 27 μm and a density of 700 kg/m^3 was used as solid material. 65% V/V aqueous solution of polyethylene glycol 4000 (PEG4000), ethanol and water were used as a binder. The results indicate that the impact of liquid surface tension and the liquid viscosity on the solids motion is significant, and the effect varies with the axial and radial position. For example, the solids circulation frequency in the horizontal plane decreases with increasing liquid bridge strength, but in the vertical plane increases with increasing liquid viscosity. In the bottom section of the mixer, solids coated with a high viscosity liquid move slower, while in the top section, such solids move faster. In the intermediate section of the bed, the solids speed decreases with the increase in the bridge strength, particularly in the region adjacent to the mixer wall. The viscous force between particles coated with PEG 4000 liquid is of mN order, while the viscous force

between particles coated with ethanol and water is of μN order. In the vertical plane, the viscosity force decreased with the increase in the bed height.

Granulation of microcrystalline cellulose in vibrofluidized bed

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The vibrofluidized bed consists of applying a vibration system to the conventional fluidized bed aiming to reduce the occurrence of bubbles, preferential channeling and defluidization phenomenon, which are common in fluidization of cohesive, adhesive and paste materials. Vibration can be imposed to the entire bed or, only to gas distributor grid. Granulation is a very important process used to increase the size of particles resulting in improvement of appearance, handling, transport of fine particles, etc. The microcrystalline cellulose is white fine powder commonly used as a stabilizer, a food additive, carrier in drugs among other industrial uses.

This paper reports the analysis of wet granulation of microcrystalline cellulose in vibrofluidized bed using an aqueous maltodextrin solution as binder. A factorial experimental design was developed with the independent variables: amplitude and frequency of vibration, pressure of atomization, inlet air temperature and maltodextrin solution flow rate. The responses analyzed were: granulometric distribution, mean Sauter diameter, percentage of lumps and flowability (quantified by the Hausner index and the angle of repose).

A statistical analysis of the process led to the optimization of the operating variables in order to obtain the desired product quality and the adequate dynamic conditions of the vibrofluidized bed. Also, the results confirmed the great potential of vibrofluidization for wet granulation, maintaining the adequate particles movement in the bed while atomizing the binding solution.

Identification of defluidization in fluidized bed coating

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The partial or complete bed defluidization is an undesired phenomenon in industrial application involving fluidized bed operations. In the process of particle coating, the defluidization can be prevented by increasing the gas velocity and/or decreasing the suspension flow rate, if the changes in the hydrodynamics of the fluidization are detected early. For industrial applications, the use of a technique that can quickly identify the region where the bed is tending to the defluidization is very important, avoiding loss of efficiency or even the necessity of shutting down the process. The purpose of the present wok is to identify the defluidization zone in fluidized bed coating process using the Gaussian mean frequency, which is an alternative methodology based on pressure fluctuations analysis.

Experiments were carried out in a Plexiglas column with a 0.143 m in inner diameter and 0.71 m in height, at temperature of 70^{o}C. Microcrystalline cellulose (MCC) of 325μm in diameter and apparent density of 980 kg/m^3 was used as fluidizing particles, which was recovered by a suspension based on Eudragit®.   All raw data sets of pressure in the plenum were collected at a sampling rate of 400 Hz, considering 2046 data points. LabView® 7.1 software was used for all data acquisition and signal processing.

The results showed that the defluidization region can be clearly identified using the methodology employed. It also could have a high potential in industrial applications, especially for on-line control in order to avoid the defluidization region and consequently the decay of efficiency of a coating process.

Pressure drop fluctuations analyses during microcrystalline cellulose in vibro and modified fluidized beds

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For all chemical and physical processes utilizing fluidized beds, it is of fundamental importance to obtain products having high level of homogeneity. In this way, stable dynamic operation of the fluidized state is necessary. Due to the difficulty of fluidizing cohesive and polydisperse materials, some modifications were applied to the conventional fluidized beds, such as: mechanical vibration, pulse of the gas input, insertion of a draft tube, etc. Also, the process monitoring aiming at detect and avoid dynamic instabilities is highly desirable to assure an efficient operation. Fast Fourier Transformations (FFT) applied to the measurements of pressure drop fluctuations have been widely used to characterize gas-solid regimes in spouted and fluidized beds as it is a simple and non-intrusive technique and can be used in a wide range of experimental conditions.

In this work, microcrystalline cellulose particles (mean diameter from below 125µm to 420µm) were granulated using maltodextrin aqueous solution (35% in weight) as binder in modified (with insertion of a draft tube) and vibrofluidized beds. FFT was applied to the pressure drop-time series obtained for different experimental conditions using both types of fluidized beds for the granulation. LabVIEW® 6.0 was the software used to on line monitor the bed pressure-drop. The objective was to evaluate the method in its capability of identifying dynamic instabilities during granulation in different equipments and for different operating conditions. The data analyses showed the viability to relate dynamic changes with dominant frequency, broadness of the spectra and proximity to the amplitude axis for both equipments.

Key words: fluid beds, power spectra, Fast Fourier Transform, dominant frequency.

Agglomeration of soy protein isolate in a pulsed-fluid bed

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Fluid bed agglomeration is commonly used to improve the instant properties of spray-dried food powders. However, the fluidization of spray-dried particles 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 soy protein isolate powder produced by a wet-agglomeration process in a pulse-fluid bed. The agglomeration experiments used commercial soy protein isolate powder (Supro® 780, The Solae Company, Brazil) as raw material. 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 0, 300, 600 and 900 rpm. The process time, atomized binder flow (aqueous solution of maltodextrin, 49% w/w, at 27 °C), atomization pressure, nozzle height and mass of sample were maintained fixed at 40 min, 2.7 g/min, 0.55 bar, 300 mm and 0.15 kg, respectively. The fluidizing air temperature and velocity were fixed at 75 ºC and 0.57 m/s. The product transformations were determined by an analysis of the particle diameter, size distribution, morphology and moisture content. During agglomeration, the raw particles coalesce, resulting in the formation of granules with increasing size, but morphological changes were also verified. The average particles size of the raw material and agglomerated product increased from 80.1 μm to 211 μm, 230 μm, 243 μm and 213 μm, at the pulsation frequencies of 0, 300, 600 and 900 rpm, respectively. Meanwhile, the product moisture varied from 4.1% to 2.9%, 4.0%, 4.8% and 3.9%, at these respective pulsation frequencies. 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 spray-dried particles was enhanced with the pulsation system, resulting in higher fluid bed homogeneity and agglomerated products with narrows particle size distribution.

Morphological characterization with image analysis of cocoa beverage powder agglomerated with steam

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The agglomeration process of cocoa beverages can transform a fine powder to granules, with modification of the product physical structure, and the characteristics of granules achieved dependent on the type of process used (agglomeration with steam, fluidized bed, thermal agglomeration), the operating conditions, the constituent ingredients of the formulation and the proportion between them. The changes in the physical structure of powder that occurs due to the agglomeration with steam, are mainly in size and format of the granules, and can be retracted through morphological analysis.

The objectives of this study was to evaluate the influence of operating conditions of the agglomeration process with steam in the physical properties (size and shape) of granules and to characterize the shape of them, describing them by way of descriptors. The cocoa beverage powders were obtained in pilot plant equipment (ICF Industrie Cibec spa, Italy). In morphological characterization was used stereoscopic microscope SZX9, coupled to a Camera Sony CCD-IRIS. The images were analyzed with the software Image-Pro Plus ® - version 4.2 for Windows TM from Media Cybernetics.

The results showed that there is no difference between the descriptors of shape (curvature, circularity, roughness and rate of appearance) in the conditions of process evaluated. It was concluded that the cocoa beverage powder agglomerated with steam have elongated shape. As for descriptors of size (area, perimeter, perimeter of the convex shape and diameter of Ferret minimum and maximum) there was difference between the conditions of process for larger granules that 600 μm. In case of minimum conditions, especially in flow solid food, there is increase in the values of size descriptors.

Study of the process parameters and the influence of sugar size in the agglomeration with steam of cocoa beverage powder

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Most cocoa beverage powder is made with sugar, maltodextrin and cocoa and may also contain milk powder and whey. The amount of cocoa used in the formulations, in general, ranges from 5 to 20% and is enough to become the beverage powder insoluble and difficult to reconstitute in liquid, water or milk. A process that can be used to improve the properties of reconstitution in liquids of these cocoa products is the agglomeration with steam.

The purpose of this study was to evaluate the effects of the main variables in the process of agglomeration with steam (vapor pressure, temperature of the air of the rotary dryer, flow of solid food and the velocity of the rotary dryer) on the physical and physical-chemical properties of cocoa beverage powders (moisture, average diameter of particles, wetting time, insolubility and color - L * a * b *). It was used a pilot plant equipment (ICF Industrie Cibec spa, Italy) and it was employed the method of fractionated factorial design to evaluate the effects of process variables on the responses.

The results indicated that for the product formulated with sugar crystal, the increase in vapor pressure, the temperature of the air of the rotary dryer and the velocity of the rotary dryer implied an increase in the size of the granules. The increase in the flow of solid food has led to a significant decrease in the average size of product obtained and the increase in temperature of the air of the dryer resulted in increased insolubility, due to the formation of solid bridges more resistant and more difficult to solubilize, formed between the insoluble compounds of cocoa solids and sugar crystals. For the cocoa beverage powder formulated with sugar milled, the variable process that has had the greatest impact it was the flow of the solid food, because for a constant pressure of steam, the higher flow of solid implicates in a small granules formed.

The process of agglomeration with steam has led to an increase in the quality of the product, increasing the diameter of particles and decreases the wetting times, and these effects observed mainly in product formulated with ground sugar, due to greater surface area exposed to steam. It was conclude that the cocoa beverage powder changed color with the agglomeration with steam, presenting a decrease in brightness (L *), an increase in red tones (a *) and yellow (b *) for both products studied, with sugar crystal and ground.

Texturation of a bulk bed of wet agglomerates under vertical vibrations

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Wet granulation, usually performed during a mixing/wetting stage, is the first step of wet process elaboration of granular materials. After this first step, the medium is generally subjected to complementary stresses ensuring its final shape and/or texture. During this operation, agglomerates acquire morpho-granulometric and hydro-textural properties influencing that of the bed bulk. Bulk compacity is the more important characteristic regarding compaction and flowability in hoppers or conveying systems for example. Hoppers and conveying system ensure the transport between the different unit operations but also induce segregation and densification because of vibrations.

The objective of this work is to study the densification kinetic of a bed bulk of wet agglomerates according to water content. These experiments are realized on three raw materials currently used in several industrial fields (kaolin, cellulose microcrystalline and calcium phosphate) after a wetting/mixing stage in a planetary mixer. The densification is recreated thanks to a volumenometer generating normalized taps.

Experimental kinetics are compared to that given by a model specially developed to describe, between the dry and the saturated state, the densification of an agglomerates bed bulk, at each water content. The proposed equation is not empirical and has its roots in a micro-scale approach developed by Boutreux and De Gennes (1997). It generalises the well-known “Chicago’s law” (Knight *et al.*, 1995), and gives a physical signification to all these parameters. Moreover, we show that for each number of taps, the solid volume fraction follows a texturation phenomenon according to water content. This phenomenon highlighted by our experiments has never been observed before and is an original result of our work. A mathematical law is proposed to model it, and the association of this equation to the kinetic model, make it possible to represent the densification of a bed bulk of wet agglomerates on a state surface : solid volume fraction versus water content/number of taps.

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Fractal morphogenesis description of agglomeration in low shear mixer

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Wet agglomeration is a widely used process in the industry for its numerous advantages like: (i) reduction of dust production, (ii) enhancement of the flowability, (iii) bulk density increase, (iv) reduction of segregation.

Three raw materials: kaolin, microcrystalline cellulose, and phosphate calcium, usually employed in various industrial sectors, are mixed independently with distilled water. Agglomeration trials in a low shear mixer are analyzed. The evolutions of morpho-granulometrics and hydro-textural parameters of the agglomerates resulting from the operation of wetting/kneading within a planetary mixer, are carried out. The textural properties measured at the agglomerate scale are compactness, saturation degree and water content. These are plotted on a phase diagram, called an hydro-textural diagram defined by Ruiz and al (2005), and represents the elaboration path of the agglomerates. The granulometric distribution is measured for all the water contents which define the range of agglomerate mode: from the dry state to the pasty transition.

This experimental study shows that with increased water content, compactness of agglomerates decreases on the entirety of the hydrous domain while their diameter increases. These two parameters (compactness Φ and diameter d) are perfectly correlated by a power law:

$$\Phi \propto d^{Df-3}$$

and this, for all the diameter classes of the population ranging between the d_{25} and the d_{75}. It is shown that the exponent *Df* play the game of a fractal dimension associated with this coalescence. Whatever the population fraction considered, *Df* is constant. It does not seem to depend either on the range of pale velocity tested in this study. Moreover, for the three products the fractal dimension is quasi-identical: around 2.75, representing a dense structure within the agglomerate. The whole of these results makes it possible to strongly advance the assumption that the agglomeration process follows a morphogenesis of the fractal kind.

The classical agglomeration process theory indicates that three phases take place in the phenomenon: wetting/nucleation, consolidation/coalescence and growth, and breakage and attrition. This work brings complementary interpretations. The first phase of nucleation represents the stage during which the pattern of the fractal growth: the nuclei, are built. The stage of consolidation and growth finds a fractal character, during which the agglomerates are in expansion constantly, which not highlighted forever (!?!). It means, here, that consolidation is not observed as the increase of the compactness.

Finally, the influence of the wetting mode via the study of two kind of binder distribution (by payment and pulverization) supplements the study for the nucleation phase which is the key stage of the control of granulometric and textural properties of the agglomerates.

Wheat flour reactivity and agglomeration process: influence on growth and texture of agglomerates

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The reactivity of wheat powders is defined as particles ability to react under exterior constraints (water adding and mechanical/thermal energy contribution). This reactivity is considered in regard with “Intrinsic Characteristics” of flour particles: size and shape, wettability, surface chemical composition, etc. Therefore, the behavior of wheat powder particles have a significant role during the agglomeration process after kneading and wetting, which results in the formation of agglomerates or a crumbly dough at higher water contents.

So far, no studies have been conducted on the agglomeration mechanisms of wheat powders. On a double-approach basics, we tried to analyse the hydro-textural and the morpho-granulometric parameters of agglomerates produced in various operating conditions. Two wheat flour powders (flour and semolina) were prepared by milling durum and soft wheat respectively. These powders are usually used in preparing two different types of cereal products: pasta and noodles. The milled wheat varieties were selected to get relatively two different powders in their physical and chemical properties.

The agglomeration processes of wheat powders were observed through the evolution of morpho-granulometric and textural parameters along with water content. Textural parameters were observed on two scales: the agglomerate scale and the bed bulk scale. These textural parameters were evaluated via the measurement of the agglomerates solid volume fraction, and those of the bed bulk solid volume fraction respectively. Additionally, the used mixer was equipped with a power-meter to measure the power consumption during the agglomeration processes and thus the changes in the medium consistency.

The obtained results have showed that the agglomeration mechanisms for wheat flour and semolina were almost similar to some low reactive powders. Also, agglomerate growth can be expressed by two major parameters : a mass fractal dimension, and the compacity of the nuclei which are the initial generators of an agglomerate structure. These parameters are significantly dependent on the powder reactivity. Besides, we could define the transitions limits between the three stages: (powder, agglomerate, and dough) on the hydro-textural diagram of the mixture. These results, established a fundamental method to characterize wheat flour agglomeration process and suggest further explorations of its potential use in various powders applications.

Assessment of granule strength via surface energy and densification approaches

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High shear wet granulation (HSWG) process is lacking of fundamental insight. This has precluded the identification of a standardized method for the determination of start-point and end-point detection. It is suggested that previous attempts of start-point and end-point identification have failed due to a lack of understanding with regards to the granule characteristics of interest. Clearly, this requires, for example, a deeper appreciation of the granule formation and characterization.

The ability to describe the state of granule consolidation and granule strength is extremely important in the area of pharmaceutics. It is believed that this work demonstrates that it is possible to monitor the granulation progression in terms of in-process granule densification. This provides better understanding of the densification process of granules during high-shear wet granulation.

Of particular importance are granule structure and interparticle forces that contribute to agglomerate strength. This work assesses the surface energy of the starting materials and granules that will lead to a quantified theoretical determination of final agglomerate strength. Preliminary results on surface energy offer the dispersive component of materials in order to understand the compact experiments that yielded some behavior rendering by the polymeric material. Granulation monitoring using NIR was collected during the granulation process to monitor the densification of granules; the wet massing portion of the experiment was evaluated. Finally, the importance of agglomerate strength is linked to densification during processing and particle size measurement techniques will be discussed. All is directed with the eye on determination of start-point and end-point detection by understanding the granules formation.

Multi-scale modeling of particle flows in granulators

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Recently efforts have been made to couple discrete element method (DEM) and population balance (PB) models to predict granulation process performance. These studies have attempted to combine the strengths of DEM for modeling particle-scale phenomena such as collision frequency and collision velocity distributions, with the strengths of PB models for modeling macro-scale granulation processes over longer time scales. In this paper we present a different approach to combining DEM and PB models. The DEM model is used to generate an intermediate compartment model of particle flow through the spray zone of a paddle granulator, which can then in turn be easily used within a PB model framework. The compartment model presents a greatly simplified, but still accurate, description of the particle residence and circulation times in the spray zone. The development of the DEM model and corresponding compartment model will be presented.

Design of regime separated granulation

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Currently, many of the granulation rate processes occur simultaneously in industrial applications, making it difficult to control product properties, such as size and density. These three rate processes include wetting and nucleation, consolidation and growth, and breakage and attrition. The aim of this research is to physically separate the different rate processes to get better control of the product granule attributes.

A new design was developed that incorporates the wetting and nucleation, and also the consolidation and growth mechanisms in two separate pieces of process equipment. The first piece of equipment is a conveyor belt apparatus that achieves monosized nuclei granules from monosized drops on a bed of powder. Following nucleation, the granules and fines are transferred to a tumbling drum, where they densify and grow by layering of the fines. By separating the two rate processes, extremely tight control of the granule size and density is achieved. Results for the granulation of two different model powders using this new regime separated granulation process will be presented.

Scaling rules for high shear granulation: a case study for pharmaceutical granulation

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The current work is a case study for determining the scaling rules for pharmaceutical granulation as a part of major project that aims improving pharmaceutical product quality by determining optimum design space and scale-up rules for specific operations and their processes as a whole. This study allows recent approaches to be critically tested with real pharmaceutical formulations. Gabapentin is used as the API to be granulated along with some excipients. Characterization of the formulation properties combined with reasonable estimates of process parameters are used to calculate key dimensionless groups available from existing models in literature. Experimental conditions for laboratory scale experiments were determined by using these key dimensionless groups and placing the operation conditions on the regime map. The base case for the experimental design is drop controlled regime for nucleation, induction growth regime for growth and consolidation. Extreme experimental conditions are also tested to identify the risks of ending up with undesired and unstable products. Products obtained from different operating regimes are evaluated in terms of their size distribution, envelope density and bulk density, dry strength. Also distribution of gabapentin with granule size, and its chemical degradation as well as physical characteristics that correlate with gabapentin chemical stability will also be presented. Plant scale experiments designed according to the key dimensionless groups allow us to evaluate alternative scaling rules.

A bed-state oriented, new data acquisition method of fluidized bed granulation

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The data recording system of the laboratory, pilot and industrial scale fluidized bed granulators makes available the temporal changes of many parameters that make possible the analysis and the comparison of the various technologies. In addition, the recorded data give a good basis for the identification of the simulation model, as well as the model based essential secondary characteristics.

In this study 20 laboratory, 150 pilot and 10 industrial size granulations were analyzed. The analysis covered three typical families of products, in two different machines (with cyclical and continuous dust removal from the mechanically shaken sacks, and from the metallic filters by pressure shocks, respectively).

Based on the elaborated data, we found an essential functionality that is invariant to the various raw materials, and to the dimension of the unit. The bed-state diagram describes relationship between the motion and the agglomerating ability (“stickiness”) of the bed. The “bed-state diagram” helped to understand many apparently contradictory experimental observations, resulting explanations adequate to the practical experiences. Computer programs were prepared for the appropriate evaluation of the laboratory, pilot and industrial size granulation processes.

Bed-state diagram based scale-up of fluidized bed granulation

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There are two extremely different approaches for modeling and simulation of fluidized bed granulation in the literature.

One type of models, starting from the detailed description of elementary processes, derives a system of partial integro-differential equations (population balance) for the description of changing particle size distribution and of other physical properties. Because of practically unavailable physical parameters the industrial application of these models is very difficult.

The second approach, utilizes empirical relationships, measured in laboratory and pilot equipments of various size. These relationships, combined with heuristic rules are used to support the solution of practical programs. These empirical models are often not invariant to the equipment size. Consequently, the general expert rules used to be combined by the intuitive conclusions about the various materials, while some important knowledge (e.g. about the heat capacity of the construction material) cannot be taken into consideration.

In this study a practically usable, intermediate solution has been elaborated, based on the so-called "bed-state diagram". This essential functionality describes the relationship between the motion and the agglomerating ability ("stickiness") of the bed.

The applied generic simulation model describes the state elements and the elementary transitions of the processes. The resulted simulation tool describes the heat balance (including also the heat capacity of the construction material), the solvent balance, as well as the elutriation of the solid particles to the filter, as well as their cyclic or continuous removal. The particle size distribution and other appropriate physical properties are guaranteed by the well-shaped bed-state diagram in implicit. According to the preliminary applications, the bed-state diagram based method affords practical help for process design and scaling-up.

Moisture balance calculation– what is it good for? Theory and industrial praxis

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In chemical industries component balance is basic information, generally used and has a distinguished role. In particle formation processes the moisture balance that represents the most specific component balance is not as commonly used and is much less attention paid.

In the previous paper [1] a method was developed to evaluate and analyse process parameter data collected by computer controlled equipment of pharmaceutical fluidisation granulation and filmcoating processes. It was shown that in case of measuring inlet and outlet air humidity moisture balance calculation is possible and some theoretical investigation was done to understand the accuracy and probability of moisture balance measurement and calculation.

In this paper the recognised significant difference between the loss on drying results of the product (granule or filmcoated tablet) and the integral moisture balance calculated during the granulation or filmcoating process was investigated detailed and answers to the following questions were looked for :

1. Which process parameters based on error propagation of theoretical approach influence the accuracy of moisture balance calculation most significantly?
2. What is the resolution and accuracy of different process parameters collected by the pilot equipment used?
3. What form and the accuracy of equations useful for moisture balance calculation are available and what difference do they result in the moisture balance?
4. What characters have the different sensors (and measuring loops) used for humidity measurement based on different physical phenomena got?
5. What kind and measure of errors the design and operation of different equipment can result?
6. What tendency have the long term behaviour of measurement results got?

There are some examples taken on fluid granulation in Hüttlin HKC-TJ-50 and Glatt WSG 15/60 and some on filmcoating in Driam DRC Vario 500 / 600 and Glatt GMPC II equipment and analyzed detailed.

The necessity and measure of possible modifications and development in equipment design, sensors application and equipment operation are investigated and described to form the moisture balance calculation as a specific tool to characterise and compare equipment and processes helping to produce more uniform quality products.

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A systematic study of the distribution of force between agglomerates during uniaxial compression

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Compaction of granular material is a widely used manufacturing method in numerous industrial sectors. This unit operation has traditionally been investigated by using global compression or compaction equations, but the interest in macro- and micromechanical analysis has increased during recent years. It is a well-established experimental fact that an applied load is unevenly distributed between the particles, resulting in the formation of force chains surrounded by dormant regions.[1] Although this phenomenon has been extensively investigated for idealized systems containing either hard or elastically deforming spherical particles,[2,3] much less is known for the granular materials used in industrial applications.

The current work reports experimental data pertaining to the distribution of force between mm-sized roughly spherical agglomerates during uniaxial compression. All agglomerates were produced via wet granulation, extrusion and spheronisation. The agglomerates were composed of microcrystalline cellulose and a combination of microcrystalline cellulose/polyethylene glycol. The force distribution data was obtained by using the carbon paper technique, which relies upon carbon paper as the medium for transferring imprints from compressed particles onto photo quality paper, in conjunction with image analysis.[4] Systematic investigations were performed to test for effects of lubrication, material properties and porosity.

Lubrication was found to have a minor effect on the force distribution observed at low applied pressures, which however disappeared once the pressure was increased. This finding suggests that friction/cohesion does affect the initial particle rearrangement, whereas confinement dominates the constrained dynamics at higher pressures. The mechanical characteristics of the agglomerates had a more pronounced effect on the obtained force distributions, which may be interpreted as resulting from differences in agglomerate yield stress and porosity. The results obtained from these investigations show that the carbon-paper technique is able to deliver useful micromechanical information for confined compression of plastically deforming agglomerates. This information may be used to elucidate the validity of computer models of force transfer and compression, and may also provide greater insights into the processes occurring during compression of granular materials.

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Degree of compression as a process indicator of tablet tensile strength

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In order to move towards a more science based approach to solid formulation, in accordance with the Process Analytical Technology (PAT) initiative, an improved mechanistic and theoretical understanding of pharmaceutical processes and material behaviour during manufacture is critical. A better understanding of factors that control the end product and also, how indicators of such factors can be monitored in real time during production is of equal importance.

The tensile strength of tablets is a product property which is specified and monitored during tablet production. It has earlier been suggested that the plasticity of single granules is a key factor for the compactability of the powder material [1] and an increased degree of deformation of single granules expressed during the compression has been shown to increase the tablet tensile strength [2]. It would be interesting to correlate the plasticity of granules with a process indicator that easily could be measured during production. The compression parameter *a* derived from the Kawakita equation [3] has been suggested to reflect the plasticity of single granules [4] and in mathematical terms the parameter *a* represents the maximal engineering strain of a powder bed during compression. To assume that the degree of compression of a bed of granules could potentially be used as an indicator of the tablet forming abilities of the material therefore seems reasonable.

The aim of this work was to investigate the suitability of the degree of compression as a process indicator of the tablet tensile strength. Since also other factors than the plasticity of granules, such as the granule shape, can influence the degree of compression during tableting and consequently the micro-structure and the tensile strength of the formed tablets, a series of granulated particles with a variation in size, shape and porosity were prepared by wet granulation. Microcrystalline cellulose was used as a representative excipient. Tablets were prepared from the various types of granules and the relationship between tablet tensile strength and three different potential process indicators was studied.

The results indicate that the degree of compression is a better indicator of tablet tensile strength than both the applied compression pressure and the total tablet porosity (*in die* data). The degree of compression would therefore be interesting to measure in-line during manufacture to get an assessment of the mechanical properties of the produced tablets. This type of knowledge may contribute to an adaptive production of solid dosage forms with a more consistent product quality.

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Time scale analysis of fluidized bed melt granulation

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This paper describes the development of a computer model that predicts aggregation behavior in fluidized bed melt granulation (FBMG) processes. In FBMG processes, the molten binder entered at one or more points and droplets were then distributed around the bed, these processes were necessarily spatially inhomogeneous. Granule-granule collision time scale, droplet-granule collision time scale, droplet spreading time scale, droplet solidification time scale were four time scales identified as the events affecting the granulation rate.This paper presents a series of experimentally validated sub-models to describe time scales of events leading to aggregation.

Computational Fluid Dynamic using a twin-fluid model was used to calculate granule-granule collision time scale and droplet-granule collision time scales. A Volume of Fluid method was used to calculate binder spreading time scales. A dynamic energy balance was used to calculate binder solidification time scales. Validation of the twin-fluid model was done by comparing fluidized bed pressure time series with experiment. Validation of spreading model was done using high speed images of binder droplet spreading. Validation of solidification model was done using high speed infrared images of binder droplet solidification on glass plate. Granule-granule collision time scale per particle was in the region of 0.01s. Binder spreading time scale was related to contact angle, surface tension and viscosity. For PEG1500 on glass ballotini, spreading time scale was less than 0.001s. Binder solidification time scale varied from 0.005s to 0.01s. This wider variation for solidification time scale was caused by the effect of fluidized bed operating temperature. The CFD results showed that increasing fluidizing air velocity decreased particle-particle collision time scale. A spray characteristic length scale was identified from the number balance. From the ballistic droplet model, the spray active region was 14mm.

The models presented here relate sub-events of aggregation process to binder characteristics, bed temperatures and fluidizing air velocities.

Effect of batch size on mechanical properties of granules in high shear granulation

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The batch size in a granulator has a profound effect on the flow patterns. DEM simulations reported by Terashita et al. 2002, showed that the fill level influences the velocities of the particles velocity and the kinetic energies. Work done by Bock and Kraas, (2001) also established that the granule size distribution is a function of the fill level. In the current work, the effects of the fill level was examined by varying the total mass of the granulate material without changing the other variables such as the impeller speed, granulation time and liquid to solid ratio. Granules produced in a high shear mixer from pharmaceutical typical pharmaceutical excepients such as lactose, starch and hydroxyproplycellulose were used in this study. Interestingly for the same granules size increasing the batch size increases the average granule strength, for instance changing the batch size from 2000 to 2800 g has an effect of increasing the average granule strength from 0.06 to 0.13 MPa. It was also observed that the batch size also have an influence on the granule shape and packing properties.

Keywords: Batch size; fill ratio, compression, granules strength, compaction energy

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Effect of impeller speed on mechanical properties of granules

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Impeller speed is one of the most critical process variables that affect the properties of the granules produced in a high shear granulator. Several works can be found in the literature that discusses the influence of impeller speed on granules size. For example, it has been reported that the size increases with increasing impeller speed (Knight, 1993, Knight et al., 2000), while others have observed a decrease (Schaefer et al., 1993, Ramaker et al., 1998). This work focuses on the effect impeller speed on the mechanical properties. This is important because of the performance of the granules on downstream processes such as transportation and handling; depend on the mechanical properties of the granules. It was found out in this work that the response of a granulation process to changes in the impeller speeds depends on the binder viscosity. Consequently, the two extreme cases, of a low and high viscosity binder were investigated. For the low viscosity binder, it was observed that the granule strength decreased with increasing impeller speed whilst for the high viscosity binder the opposite was observed. The shape and structure of the granules is also affected by the impeller speed and this has in effect on the packing and flow properties of the granules.

Keywords: Impeller speed, granules, packing, strength

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Coupling of CIP and DEM: Particle-liquid interaction

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Liquid plays a very important role in the field of powder technology, especially in granulation and coating processes. In these processes, liquid is added to powder and the mixture is agitated to obtain particle agglomerates or liquid-coated particles.

Discrete Element Method (DEM) is a powerful tool to simulate particulate flow and is capable of providing the detailed information, which may be difficult to obtain from experiments and other numerical methods. DEM is well developed for dry and coarse particle systems where complicated inter-particle forces can be negligible. There are only a few works reported incorporating liquid motion and liquid bridge force into the DEM simulation [1], and most of the existing models are subject to various restraints e.g., the model is only applicable for pendular bridges.

In this work, the liquid motion is directly simulated using continuum approach (e.g. CFD). In granulation and coating, the boundary face of solid-liquid-vapour can easily deform and this is in general difficult to simulate. The Constrained Interpolation Profile (CIP) method [2], which is capable of treating the large boundary deformation of the inter-phase, is used for the liquid phase calculation. This work applies a DEM and CIP coupling method for the simulation of liquid spreading between particles. Several simple simulations have been completed and the result was verified experimentally. Using this method, the liquid dispersion onto the particle bed is examined.

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Simulation of liquid dispersion in dynamic powder bed inside a mixer using DEM-CIP coupling method

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In granulation and coating processes, liquid is added to powder and dispersed by mechanical forces. In these processes, it is crucial to understand the liquid dispersion since it can significantly influence the quality of the final products, e.g., insufficient liquid dispersion causes broad size distribution in granulation, and causes further agglomeration in coating processes.

In this work, the liquid behaviour in a mixer is simulated using CIP (Constrained Interpolation Profile) method [1]. It is generally difficult to simulate the liquid dispersion taking place in granulation and coating processes since the solid-liquid-vapour boundary can easily deform. CIP method is regarded as a universal method to deal with multiphase flows, and is now beginning to be applied in the field of Powder Technology. The powder phase is agitated by the impeller, and its behaviour is simulated by DEM (Discrete Element Method). CIP method and DEM are coupled in order to consider the interaction between the liquid phase and the powder phase. The relationship between the liquid properties, such as viscosity and surface tension, and the powder movement is investigated.

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Affect of spray location on coated granule quality

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Granules coating processes are common in industries such as pharmaceutical, food, fertilizers and detergents manufacturing. There are two main techniques of fluidised bed coating were used to coat the granules: top-spray fluidised bed coating and bottom-spray (Wurster) fluidised bed coating processes. In this work, the granules were prepared in a high-shear granulator (Romaco Roto Junior), and are coated used both of these methods in order to compare their effectiveness. The present study used two methods a dissolution test and SEM to quantify the quality of coating. Other parameters that will influence the quality of coating were also studied. These are fluidizing air flow rate, atomizing air pressure, mass of bed, spray rate, size of granules. The results found that all operating conditions except atomizing air pressure had the same effect on coated granule quality for top-spray fluidised bed coating and bottom-spray (Wurster) fluidised bed coating processes. Both dissolution test and SEM results showed that bottom-spray is thicker coating than top-spray fluidised bed coating.

Keywords: Fludised bed coating, top spray, bottom spray, coating quality.

Effect of internal lubricant on granule and tablet properties

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Lubrication is a vital step in the tablet production process as it reduces the friction between the die and granules or powder particles. There are two ways in which a lubricant can be introduced to the formulation being compressed into tablets; internal addition – where the lubricant is mixed with the primary powder before granulation or external addition – where the lubricant is added to the granules after granulation. The internal lubricant method is commonly used in dry granulation and there are no reports in literature on the application of this method in wet granulation. This paper compares the effect of both methods of lubricant addition on the tablet strength and dissolution of the tablets.

Result obtained show that the internal lubricant improved the flow of the granules and the strength of the tablets. Presence of the lubricant in the granules also affects size distribution of the granules and granule dissolution. It induces breakage in the granulation and reduces dissolution rate of granules. Tablet produced by internal lubricant have higher strength and lesser elastic recovery than external lubricant tablets. The dissolution rate of tablet increases in the order; without lubricant, internal lubricant followed by externally lubricated.

Key word: lubrication, internal lubrication, granulation, tablet.

Correlation of static drop-powder interaction to granule nucleation behaviour in a high shear mixer

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Nucleation is the term used for the mechanism taking place at the very early stages of granulation during which the powder and binding liquid first come together in the high shear granulator, and interact to form larger particulate entities knows as granule 'nuclei'. This process of granule nucleation, and how constituent material properties and operating conditions will affect its kinetics, is not currently well understood [1].

When one drop penetrates quickly enough the nucleation mechanism is termed *drop controlled* [2]. This means that one drop will form one granule nucleus. A narrow size distribution of drops landing on the powder surface will therefore produce a correspondingly narrow size distribution of nuclei (and other properties such as binder content, strength etc). This distribution of properties is mirrored in the final granules [3,4], making drop controlled nucleation highly desirable from a product design perspective. Conversely, if drops are not able to penetrate fast enough, then the liquid collects at the surface under the spray zone and forms a 'cake', binder must be distributed mechanically and the corresponding nuclei size distribution tends to remain broader [2].

It is reasonable to deduce that drop penetration times are related to the properties of the binding liquid and powders involved, such as particle size, viscosity and the balance of the surface energies involved etc, though as yet there is little understanding of how we can make an appropriate choice of binder and powders for a given result. Prediction of these interactions could dramatically reduce the need for expensive trial and error based formulation/process optimisation.

In this work we expand on the work presented by Ax et al. [1] which focussed on relating drop size to nuclei size in both static and mixer environs. To investigate the combined effect of drop size and liquid properties and powder properties, we used aqueous solutions of Kollidon 30 (BASF SE, Ludwigshafen) of varying concentration (0-20% m/v) as a binder and lactose of varying particle size, Granulac 230, Granulac 140 and Sachelac 80 (Meggle). The binder was added single drop-wise to a purpose built step-mixer such that nuclei could be retrieved at precise time intervals, under different operating conditions (rpm). This allowed the evolution of the nuclei size, mass, morphology and structure, to be mapped for each condition and linked to static bed results.

In conclusion, this paper presents a detailed study of the effect of binder properties, drop size and powder particle size that correlates static bed interaction to that taking place in a high shear mixer, moving one step closer towards predictive process/product design.

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Drop impact, spreading and penetration into deformable powder substrates

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Granulation is a Unit Operation (used primarily in pharmaceutics, food, agrichemical and personal care industries) which uses a liquid binder to form inter-particle bonds and agitates the powder liquid mass to promote liquid dispersion and promote granule growth, and comprises of a number of micro-scale processes such as nucleation, coalescence and breakage [1]. The powder/liquid mass is agitated to promote liquid dispersion and granule growth. Well controlled granulation produces granules of a composition equal to the overall composition of the bulk. This means that the granules can then be used in processes which are highly sensitive to composition and structure, such as pharmaceutical tablet production and flavour delivery in food products. Wetting and nucleation are the first mechanisms [2] to take place; this is where the liquid and powder first come into contact to form a granule 'nuclei'. When one drop penetrates quickly enough the nucleation mechanism is termed *drop controlled* [3]. A narrow size distribution of drops landing on the powder surface will therefore produce a correspondingly narrow size distribution of nuclei (and other properties such as binder content, strength etc). This distribution of properties is mirrored in the final granules [2,4], making drop controlled nucleation highly desirable from a product design perspective.

To date the kinetics of binder drop-powder interaction in a high-shear mixer are not well-understood. Moreover, current theory for static bed penetration doesn't capture the complexities of surface structure and pore interconnectivity [5]. This paper presents a detailed and comprehensive study of drop penetration, including detail of the rate limiting wetting stage, into powder beds, for a broad range of porosities. Various binders with drop diameters approx. 300µm to 3mm are dropped from 10mm onto beds of different powders at various porosities. The variation of contact diameter, contact angle and remaining drop volume, as well as total penetration times are captured using a high speed camera at frame rates of 250fps- 6000fps depending on the binder-powder combination. Results for varying drop: particle size-ratio coupled with viscosity, are particularly insightful.

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Twin screw extrusion: Granule properties

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Granulation is an important particle-size enlargement process used in many applications. Typically it is carried out either as a batch, or continuous process. The technique of using a twin screw extruder has been found to very effective at granulating and is an attractive proposition for manufacturing processes because it can be operated continuously. The quality of the granules produced is consistent but is dependent on many different variables. In this paper, the effect of varying the screw speed, solid feed rate and the method of binder addition are investigated.

Whilst previous works report mainly on the effect of the screw speed or solid feed rate (Keleb et al, 2004, B. Van Melkebeke et al, 2008) this work focuses more on the effect of the addition method of the binder, either wet in a solution with water, or dry as a powder mixed with the carrier materials, where water is added later. All other conditions remain unchanged for each variable being investigated and the formulation used throughout is kept constant. This paper shows that all three process variables (the method of binder addition, screw speed and solid feed rate) have significant effects on the distribution of size, shape and structure of the granules. For granulation adding water, granules were produced with a higher ratio of powder to binder, whereas for wet granulation adding Hydroxypropyl Cellulose (HPC) solution, the granules were larger and the ratio of powder to binder was reduced. Both techniques resulted in irregular, non-spherical shaped granules.

The granule properties of each variable were tested and compared to determine what the most suitable method of granulation is for a twin screw extruder, using this formulation. The ideal method will give strong consistent granules, which is important for reliable process operation.

Binder addition methods and binder distribution

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Fluidised Beds and High Shear Mixers are both important pieces of equipment in the granulation process. Binder addition method affects the growth and properties of granules and is therefore of vital importance to the understanding of this detailed process [1 and 2]. There are currently two main methods of adding the binder during granulation, dry or in solution, which are commonly used in the pharmaceutical industry.

This paper compares the two various binder addition methods, wet and dry, in both a High Shear mixer and Fluidised Bed granulator. The binder was traced throughout each process over time using industrial colouring dye and UV Spectrometry. The dissolution rate of the granules was tested as well as their size and strength.

In this paper the two methods, dry and wet, in a Fluidised Bed and High Shear mixer were used to successfully produce granules with a typical pharmaceutical size which all exhibit varying trends of liquid to solid ratio over varying size classes. For wet addition of the binder in both the Fluidised Bed and High Shear mixer binder content increases with size class. However, for dry addition in both pieces of equipment binder content remains constant throughout varying size classes.

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Optimisation of variable high shear mixer conditions in a group design project

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High shear mixers are commonly used within pharmaceutical, plastic, ceramic and food industries for the production of granules. This paper reports an undergraduate design project for the production of high quality tablets from granules. In this, the relationship between high shear mixer process parameters and granule properties was studied. The group investigated the effect of variable impellor speed, water mass and addition rate on the size distribution, bulk density, flowability, strength and appearance of granules. The formulation chosen for granulation consists of Lactose, Microcrystalline Cellulose, Ac-Di-Sol Croscamellose Sodium and dry added Hydroxyprophyl Methylcellulose. Conclusions derived from the analysis of the granules provide the justification for the implementation of specific unit processes that improve the quality and production of homogeneous pharmaceutical tablets. A key element of the project is to consider the entire process from raw material to final tablet product, and to enhance the efficiency by improving continuity.

Keywords: design project, high shear granulation, granule properties, product quality

Granulation of food powders: unsteady granular velocities

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Previous work performed on the influence of liquid properties on bulk granule velocities inside a high shear mixer were carried out under steady state conditions [1]. However, bulk granule velocities inside a high shear mixer are unsteady. This is because granule properties; size and surface liquid content change with granulation time. Thus a granulation process should be represented by a series of unsteady bulk granule velocities. This work looked to further understand the influence of liquid binder properties on the unsteady state granule bulk velocities with granulation time. Particle Image Velocimetry was performed on high speed recordings of bulk granule movement inside a high shear mixer. The material was a multi-component mixture provided by Nestlé.

Further work looked at relating the granule velocities to aggregation rates within the granulator. Particle size was obtained from samples at relevant times in the granulation process and put into a Population Balance Model to obtain aggregation rates. Being able to couple the liquid properties to the particle velocities and aggregation rates of a granulation process should allow for better understanding and could hence be a valuable tool for the granulation industry.

Keywords Granulation, Liquid viscosity, Surface tension, PIV

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The chemometrics of granulation - during the process?

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The use of chemometrics to study the incredibly detailed and complicated multi-variate systems commonly encountered in high-shear wet granulation is little practiced within academic circles. Within the pharmaceutical industry, chemometrics is well embedded as a method of analysing data and drawing effective conclusions, however this is commonly practiced in more of an experimental design arena, instead of aiming at achieving statistics on the granulation process itself.

This presentation looks at a set of experiments with novel data collection methods at their core, designed to be highly repeatable, and very well controlled. Much data is collected on the physical state of the granules, both "in process" (online), via sampling during the granulation, and also at the end of the procedure.

Data collected, includes material characteristics and process "input" data. In process data including novel multi-variate data, granular size (in granulator), and univariate, more conventional, power, temperature and humidity data for the granulator. Drying, moisture content data, and offline size information is collected from samples taken regularly during and at the end of the experiments. These studies are backed up with extensive method development and characterisation and calibration of the instruments used.

The results show how repeatable granulation can be in a carefully controlled environment and detract from the common assumption that granulation is an inherently random and stochastic process. The breadth of the data collected along with its assessed accuracy strengthens the argument that much of granulation variability can be explained by small yet significant variations in input conditions.

These results help to propose a standard analysis route for granulation, shows the power of chemometrics to understand the product under study, and how this is to be used to assess the repeatability of a traditionally viewed stochastic process.

An investigation of the contribution of dry added HPMC to a wet granulation of pharmaceutical materials in high shear mixer

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In pharmaceutical industries, HPMC is one of the most common binders used. During the granulation process, HPMC is normally mixed dry with other ingredients and water is used as granulating liquid. The HPMC added dry hydrates with water added, and becomes the main source of binding forces between particles. Therefore, it is important to understand the development of the hydration processes and the process parameters that may influence this process.

This paper presents an experimental investigation of the hydration process and its impact on the granulation process. It was found that the degree of the hydration of HPMC is one of important factors determining the particle size growth and formation of lumps (oversized granules). The development of the hydration was promoted by the amount of water added, the intensity of agitation, the rate of water addition and the massing time.

Key words: wet granulation, high shear, hydration, HPMC

Characterisation of impact stress from main impeller act on granules during granulation processes in a high shear mixer

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In wet granulation processes, the powder mass and/or granules experience impact stresses from the rotating main impeller blades. This stress has both positive and negative influence on granule growth. On the one hand, the stresses from impeller blades will promote the liquid binder distribution and compaction of the granules, which will be positive to granule growth. On the other hand, the stresses resulting from the rotating impeller blades are the main cause for breakage of granules when the strength of the granules is not sufficient to overcome them. Therefore, the granule growth will depend upon the balance between the granule strength and impact stresses caused by the impeller blades. In order to achieve better understanding the growth mechanisms in granulation, it is of critical importance to know the magnitudes of these impact stresses acting on wet mass and/or granule.

In the current paper a physical model is developed, which can be used to estimate the magnitude of these impact stresses acting on the wet granules based on impeller blade rotation speed, and its geometry, such as blade decline angle, length and width, powder loading height. The model is developed by calculating the forces required to move impeller blades in the wet powder mass to make the mass rotate at a certain velocity. The experimental validation of this theoretical model is presented and application of the model is also be discussed.

Key words: wet granulation, high shear, impact stress

Characterisation of dynamic strength of wet granules function of impeller rotation speed

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In wet granulation processes, granule strength plays important roles in particle size growth. Granules with high strength survive the intensive impact stresses and grow in size by layering or coalescence mechanisms when sufficient liquid is available on its surface. Granules with low strength break down to small fragments due to impact stresses from rotating impeller blades. It is known that the strength of wet granules is composed of two parts: static strength and dynamic strength. The static strength was described by theory developed by Rumpf (1962), in which the granule static strength was determined by granule porosity, content of liquid, surface tension of liquid binder and contact angle between the liquid and solid particles. The dynamic strength of the wet granule has been highlighted by Iveson et al., (2002). In their work, the dynamic strength was found to be function of strain rate and revealed that the dynamic strength becomes dominant over static strength at the high strain rates induced by the impact stress of the impeller blades. However, the correlation between the impeller rotation speeds with the strain rate was not given.

This paper is intended to establish a correlation between the strain rate of a wet granular specimen at different impact velocity and properties of the specimen. A cylindrical shaped wet specimen with well controlled properties dropped from different height onto a flat and rigid surface and the corresponding strain rate was measured using a high speed camera. The variables of the specimen include particle size, content of liquid binder, porosity and saturation level. The results from impact tests was also compared with compression test performed on similar specimen at different and controlled strain rate. The results from this work can be used to estimate the contribution of impeller rotation speed to dynamic strength of wet granules.

Key words: wet granulation, high shear, dynamic strength

Nanosuspension Spray-Coating System for Improving Dissolution Properties of a Poorly Water-Soluble Drug

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In general, oral administration of poorly water-soluble drugs frequently leads to variable and/or poor bioavailability. Among various pharmaceutical approaches to improvement of the solubility of poorly water-soluble agents, preparation of nanosuspensions has attracted much attention recently. In this approach, poorly water-soluble therapeutic agents are formulated as nanometer-sized particles in water with a stabilizer. The primary feature of the nanosuspension formulations is to enhance the solubility and/or the dissolution rate of crystalline drugs because of their small size in nanometer order and increased specific surface area.

Several issues to be concerned in nanosuspension formulations may be aggregation of the dispersed nano-crystalline drugs that leads to crystal growth and consequent sedimentation, and dosing convenience. Solidification of the nanosuspension formulations can give a potential advantage toward such issues. For this purpose, we have proposed a novel technology –Nanosuspension Spray-Coating System (NSCS)– to formulate the nanosuspensions into a solid microparticulate unit. Glibenclamide (GLI) was selected as a model drug. Its particle size as received was 14 micrometers, and the water solubility was 6.0 mg/L at pH 6.8. GLI was ball-milled in purified water with soybean lecithin (SL) or sodium dodecyl sulfate (SDS) and polyvinylpyrrolidone (PVP). Particle size of the milled samples was in submicron regions (0.20-0.25 μm in diameter). The resultant aqueous nanosuspension was sprayed onto lactose cores (32-106 microns) by the spouted bed spray coater to prepare the microparticles (MPs) with a layer of GLI-additive composites. The MPs were obtained at the yield of 79-89%.

In vitro release studies revealed that SDS-rich MPs showed the improved apparent solubility and the enhanced dissolution rate of GLI when compared with the corresponding GLI crystals alone and physical mixture, due to the presence of SDS acting as a solubilizing agent and a good-dispersing ability of MPs. The in vivo GLI absorption through the intestinal tract in the SDS-rich MPs was enhanced to the level that was comparable to that in the intact nanosuspension.

Non-crosslinked chitosan nanoparticles as a novel biodegradable coating agent for prolonged-release microencapsulation of protein drugs by spouted-bed spray-coating

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As a biodegradable coating agent for prolonged-release microencapsulation of protein drugs by a spouted-bed spray-coating process, non-covalently crosslinked chitosan nanoparticles (CNPs) were prepared by a novel aqueous neutralization-precipitation techinique. Chitosan with a different degree of deacetylation (DD), i.e., 84.4 and 99%, was used. Each chitosan (2.0 w/v%) was dissolved in 300 mL of 10 wt% citric acid aqueous solution. This solution was added to 300 mL of 3N NaOH aqueous solution under magnetic stirring at room temperature so as to neutralize and consequently precipitate chitosan molecules in the form of nanoparticles., microencapsulation of a model protein-drug (bovine serum albumin (BSA)) was carried out using a spouted-bed spray-coating process to evaluate the coating performance of the CNPs thus prepared. Initially BSA aqueous solution was sprayed onto inert core particles of calcium carbonate (63-75 μm in diameter). The BSA-layered particles were subsequently microencapsulated by spraying the aqueous dispersion of CNPs. In vitro release studies were performed using a paddle method in phosphate buffered saline (pH 7.4). The concentration of BSA released was determined by a micro BCA protein assay kit.

In a typical formation, mean particle size of the CNPs with 84.4 and 99% DD were 322 and 399 nm, respectively. Altering the concentration of chitosan solution was effective to control particle size of the CNPs in the range of 150 to 300 nm. Zeta potentials of the CNPs were in the range of 10-17 mV. The BSA-containing microcapsules with mass median diameter of 77 μm were successfully obtained at the yield of 90-94%. No significant agglomeration of the microcapsules was observed, suggesting the usefulness of the CNPs for making it possible to coat fine particles smaller than 100-μm diameter discretely. The BSA microcapsules showed prolonged-

release profiles of BSA. These results demonstrated that the CNPs have a potential to be a biodegradable coating agent for a microparticulate controlled-release system of protein drugs.

Spray-coating of pharmaceutical fine particles by miniature spouted-bed process

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In the formulation study at an early stage of the pharmaceutical development, the pharmaceutical processes, especially granulation and film-coating, using a small amount (several grams) of samples are often desirable because of the limited availability of the amount of a newly developed active pharmaceutical ingredient (API). In this context, one of the present authors has developed a novel miniature spouted-bed as a pharmaceutical apparatus that enables both granulation and coating in a very small batch scale (typically 3 to 10 g).

The aim of the present study is to investigate the coating performance of the miniature spouted bed for drug-containing particles with diameter of smaller than 100 μm. Calcium carbonate core particles (75-90 μm) with a layer of carbazochrome sodium sulfate (CCSS) as a water soluble model drug were preliminary prepared by a conventional spouted bed coater with a draft tube at a 200-g scale. Ethylcellulose psedolatex, Aquacoat® (AQ), was employed as a coating material, and a plasticizer (triacetin) was formulated so as to adjust the softening temperature of AQ to be 65ºC. Five grams of the CCSS-layered particles thus obtained were charged to the miniature spouted bed and then spray-coated in the following typical operating conditions: inlet air temperature of 55ºC; outlet air temperature of 30 ºC, inlet air flow rate of 10 L/min, spray air rate of 15.0 L/min, spray liquid flow rate of 0.15 mL/min. The feed coating amounts of AQ were set to be 20 and 40 wt% based on the charged amount of the CCSS-layered particles.

Yields and mass median diameters of the AQ-coated particles at 20wt% coating level were 89% and 83 μm, and those at 40 wt% coating level were 87% and 93μm, respectively. Microscopic observation revealed no significant agglomeration of the coated particles irrespective of the feed coating levels, indicating that the CCSS-layered particle were discretely well-coated with the AQ even in such a small-scale production as 5 g. Indeed, the coating layer of AQ was detected through the microscopic observation. Drug-release studies were carried out by the JP XV paddle method using distilled water as a release media. The test samples were thermally cured at 80ºC for 12 hours to make film-formation complete. The AQ-coated particles at 20 wt% coating level showed a burst release of CCSS because the feed amount of AQ was too little to achieve prolonged release in the employed formulation. In contrast, release of CCSS from the AQ-coated particles with 40 wt% coating level tended to be prolonged though approximately 50% of an initial rapid release still remained, suggesting that the more increased coating level of AQ may make it possible to prolong drug-release. While the present study demonstrated that the discrete coating of even fine particles smaller than 100 μm was possible by the miniature spouted bed, further optimization of the formulations including the feed amount of AQ will be required to prolong drug-release from the coated particles.

Analysis of particle mixing in a paddle mixer

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The use of Discrete Element Method (DEM) is rapidly expanding as a modelling tool to analyse particulate processes and to address technological needs in various compartments of pharmaceutical, food and detergents industries. Good examples are obtaining the parameters which cannot be measured or quantified experimentally (e.g. internal powder flow and mixing patterns) and facilitating the scale-up of particulate processes from laboratory to pilot plant. In spite of a significant amount of research being carried out in the area of DEM modelling, nevertheless, the validity of using DEM as a modelling technique for a realistic powder flow simulation in various industrial applications still remains a challenge. This paper summarises a report on the capability of DEM to understand the powder flow pattern in mixing process. The powder flow behavior inside a paddle mixer, run at different operating conditions (e.g. different rotational speeds and fill levels), is simulated using DEM. The simulation results are compared with the experimental measurements using Positron Emission Particle Tracking (PEPT, separately carried out at Birmingham University) in terms of spatial and temporal averaged velocities, circulation time frequency and velocity distribution. The comparison shows that DEM is capable of predicting the dynamics of the powder flow inside the mixer.

Modelling granulation and acoustic emission using the Discrete Element Method

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Granulation is used in many industries these days including the pharmaceutical, poor or improper granulation can lead to problems further down-stream such as poor quality or unacceptable products. Passive acoustics is used to monitor granulation processes, although there is a limited understanding as to how it relates to the physical state of the granules. In addition to the noise inherent to a granulator machine, the sound produced by the granulation is a result of collisions among particles, between particles and blades, and particles and walls. The frequency and amplitude of the generated sounds are affected by the physical and chemical properties of particles, the blades and the vessel wall, as well as the addition of liquid binder. Wet granulation is an unsteady-state process, so, the sound generated in the process also changes with time.

The aims of this work are to understand the relationship between the sound and various collisions as mentioned above and to use the knowledge gained in the process to better monitor and control the wet granulation process. The methodology adopted is to record the acoustic emission from a lab scale granulator, and to create a 3D DEM model with identical geometry to the lab equipment. The DEM model has been used to understand the flow patterns and particulate interactions within the system. The effect of changing process variables and granule properties were investigated using the model and the model validated by comparison with changes in the recorded acoustic emission and high speed filming of particle motion.

The aerodynamic dispersion of cohesive loose powder aggregates: the effect of interparticle cohesion on dispersion performance

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Dispersion is the desired disintegration of particle clusters down to their primary constituents through the application of external forces which overcome the interparticle attraction forces. It is used in many processes both wet and dry for the characterisation of particulate systems and, for the latter case, the therapeutic drug delivery via the lungs from dry powder inhalers (DPIs). However, the complete dispersion of fine cohesive powders in gases is difficult due to the relatively large interparticle attraction forces, such as van der Waals, electrostatics and liquid bridges, compared to separating forces arising from fluid energy. It is of great interest to study the interactions between fluid and cohesive powders and to analyse the parameters which affect the break up of loose aggregates within a fluid.

In this paper experimental and computational approaches are used to investigate the interactions between bulk powder and a dispersing fluid. Bulk powder cohesion is quantified using a ring shear tester through relating the major principal stress to the unconfined yield strength. Subsequently powders are dispersed in high pressure air flow fields using various devices and the dispersion performance is analysed. The distinct element method (DEM) coupled with computational fluid dynamics (CFD) has also been implemented to investigate powder dispersion behaviour at a particulate scale. Furthermore a dispersion model relating the force acting on a sphere to the necessary force to break a contact is introduced and implemented within the computer code.

Analysis of granule breakage in a rotary mixing drum: experimental study and Distinct Element Method analysis

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Rotary drums are commonly used in particulate solid industries for mixing, coating and reactions. The process is often accompanied by undesired breakage of granules. For this reason, they are sometimes used as an attrition testing device.

In this work, the attrition of three types of granules in a rotary drum is analysed. The granules have been produced by fluid-bed coating (size 300 to 1000 μm), high shear granulation (size 300 to 1000 μm) and extrusion (size 500 to 1000 μm). The rotary drum has an internal diameter of 0.39 m and a single baffle. Attrition tests are conducted at 18, 35 and 52 rpm for 4000 cycles. The extent of breakage is quantified by sieving out fine debris which is two sieve sizes smaller than the feed particles.

To relate the extent of breakage in the drum to granule characteristics, single granule impact tests are performed on one type of granule at several velocities. The effects of particle size and impact velocity are analysed and a power-law relationship is found between impact velocity and single granule breakage. This information is used to simulate granule breakage in a rotary drum by Distinct Element Method (DEM). The drum is simulated for 5 rotations at the rotational speeds stated above and the breakage rate per rotation is compared to experimental results obtained.

Effect of process parameters on properties of granules produced in high shear granulators

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The main objective of this work is to explore the effects of different process parameters such as impeller speed, granulation time and binder viscosity on granule size, density and strength. A high shear mixer/granulator, (Cyclomix manufactured by Hosokawa Micron B.V., The Netherlands), has been used to produce granules. Calcium carbonate (Durcal) was used as feed powder and aqueous polyethylene glycol (PEG) as the binder.

The current work shows that increasing granulation time has a great affect on granules strength, until an optimum time is reached. Increasing the granulation time leads to a more densified granule. Granule size distribution is also affected by granulation time; granules produced at the optimum time have the narrowest size distribution.

Granule consolidation becomes more extensive as the impeller speed is increased resulting in high strength and low porosity of granules. Moreover, granule size distribution seems not to be affected significantly by an increase in the impeller speed.

Granules produced with a high binder concentration have a considerably low strength with a wide distribution due to poor dispersion of binder on the powder bed.
Binder addition method has shown no considerable effect on granule strength or size distribution.

Experimental and numerical analysis of homogeneity over strip width in roll compaction

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Dry granulation of powders using a roll press is a size enlargement process that renders the powder handleable and suitable for storage and processing. The main advantages of this process are that it is dry (thus well-suited for water and solvent sensitive ingredients), continuous, and economic. However, a quantitative understanding has proved difficult to develop because the complexity of powder behavior and the large number of operating parameters.

For roll presses with horizontal feeding systems, many studies have shown that the process parameters with most influence of quality and homogeneity of strip are the operating conditions of the roll press, the mechanical behavior of the powder and the tribological properties at the contact surface between powders and rolls. Various studies have given experimental demonstrations of the non-homogeneous properties over the width of the compacted strip (Tundermann et al., 1969; Simon et al., 2003, Lecompte et al., 2005). For a better representation of powder behavior and process parameter interactions, Dec et al. (2003) used an advanced modeling with finite element method to analysis the two-dimensional powder compaction in roller press. However, due to restrictive 2D assumptions, these results could not be related to experimental observations of the property variation over the strip width.

The object of this paper is to study by experimentation and 3D finite element modeling the homogeneity of properties over the width of a compacted strip of microcrystalline cellulose.
A specially instrumented roll press was used. The fixed roll was equipped with three strain gauges over its width and without contact with the powder. Pressures and density over the width of strip were recorded and are discussed in comparison with data from the literature.

Furthermore, a three-dimensional finite element analysis was developed using the commercial software Abaqus to predict properties over the strip width due to the flow behavior of powders. The powder feed was assumed to give a constant powder throughput or a constant feed pressure.

Comparison of predictions and experimental results confirm a real capability of the approach to analyze the roll compaction process in its three dimension.

Keywords: Roll compaction; Mechanical behavior; 3D Finite element modeling

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Mixing of a wet granular medium: Particle size and liquid effects

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The mixing of a wetted insoluble granular medium is experimentally studied focusing on the variation of the mixing energy consumption with the addition of liquid and liquid distribution in the granular bulk. An adequate rheological description of mixing of a granular medium can be based on concepts developed in wet granulation processes.

During the mixing, the wetting liquid is added progressively with a controlled flow. The representation of the mixer intensity consumption as a function of the added liquid amount is used to characterise the different wetting states of the granular medium. It can also be used to study the influences of different parameters (liquid, solid or process parameters) by comparing the intensity consumption values obtained at the levels of the capillary and funiculary regimes, and the necessary liquid amounts corresponding to the capillary states.

Our first results, focusing on the influence of the particles average diameter of glass beads and calcite (CaCO3), show that the intensity consumption is function of the opposite of the particles size (for the capillary and funiculary states). However, an exception is observed at the level of the funiculary state of the calcite, for which there is no particles size influence on the intensity consumption for calcite particles average sizes inferior to 150 μm (Fig. 1.).

To understand this inhomogeneous liquid distribution through the granular medium, during the first moment of the mixing, different approach were used:

- Microscopic observations of granular samples removed at the level of the funiculary state
- Modification of the liquid flow and the number of liquid feed

In addition, the effect of the liquid viscosity and spreading of liquid over the granular medium will be presented.

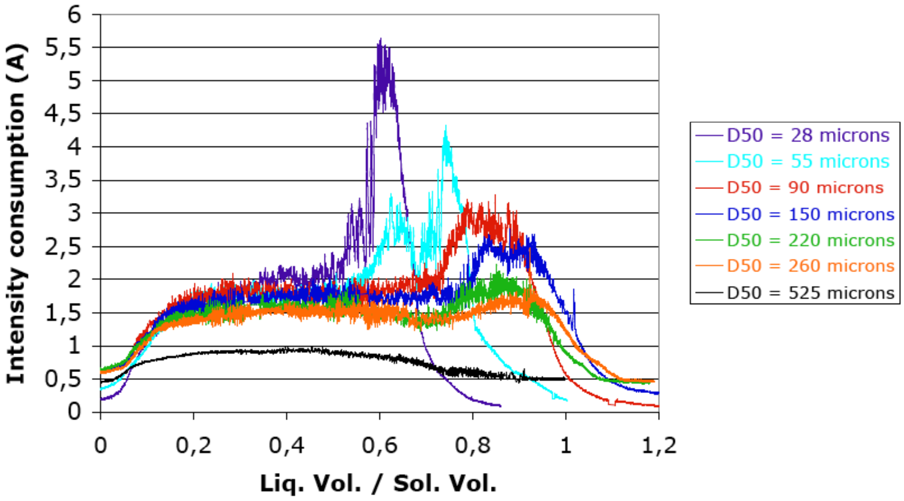

Fig. 1. Intensity consumption mixing profile of calcites for different particles average sizes

Keywords: wet granular mixing, particles size effect, liquid characteristics

Surface modification of talc particles by dry coating: influence on the wettability and the dispersibility in aqueous solutions.

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Even though dispersion operations have been the object of several investigations, the importance of the various parameters and especially the physicochemical properties and the surface modifications are rarely treated. Dry particle coating can be used to create new-generation materials by combining different powders exhibiting different physical and/or chemical properties. In such processes relatively large particles (host particles) are mechanically coated with fine particles (guest particles), without using solvents and subsequent drying, to create new functionalities or to improve 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. In this study the dry coating experiments were performed with two different processes using a high-energy impact coater "Hybridizer" (Nara) and a high shear mixer "Cyclomix" (Hosokawa). Talc particles (d_{50} = 12,4 μm) were coated with fine particles of hydrophilic or hydrophobic fumed silica (d_{50} = 15 nm).

The dispersion of powders in liquids depends on parameters involving both the process (stirring power, temperature and reactor geometry) and the material (the powder, the liquid and the powder/liquid interface). The purpose of this study is to investigate the influence of the surface modification of talc particles on their wettability and their dispersibility in water. Several powder characterisation methods have been used to study the physico-chemical properties of the coated particles. These include: observation by environmental scanning electron microscopy (ESEM), characterization of cohesion and flowability by tap density measurements, determination of wettability and surface energy by measurements of the contact angle between the coated particles and different liquids. In our case, the kinetics of dispersion of particles have been carried out using an optical fibre sensor.

Different parameters of the coating have been studied like the silica/talc ratio, the impact energy (Hybridizer) or shear velocity (Cyclomix) and the time of coating process. In the same way, different parameters of the dispersion process have been studied especially the stirring power or the surface energy of the liquid medium.

Innovative fluid bed pelletising technologies for matrixpellets and micropellets

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Pellets can be formulated to different drug products: capsules, tablets, sachets, oral liquids and ODT (orally disintegrating tablets). Especially when taste masked micropellets are the objective particular pelletising technologies have to be applied. In addition to the established pelletising technologies innovative technologies allowing new formulation options and product qualities are presented. In particular, unique benefits and opportunities such as a small pellet size range of 100 – 500 µm, uniformity of particle size distribution, smooth particle surface, high density and high drug loading are achievable.

The Controlled Release Pelletising System (CPS™) Technology is an advanced fluid bed rotor technology allowing the preparation of matrix pellets with particular properties in a direct pelletisation batch process; extremely low dosed and high potent API's can be formulated to matrix pellets as well as high dosed APIs; the drug concentration can vary from < 1% up to 90%. Inert starting beads are not required; together with the frequently used microcrystalline cellulose powder functional excipients like polymers, disintegrants, solubilizers and the like can be part of the CPS™ formulations in combination with the API. Applying a defined set of processing parameters incl pelletisation forces throughout the process a controlled release of drug from the matrix pellets is achieved.

The MicroPx™ Technology provides matrix type micropellets with a particle size < 300 - 400 µm and a drug load of typically ≥ 95%. Functional pharmaceutical excipients, e.g. for bioavailability enhancement or controlled drug delivery can be integrated in the pellet matrix. The formulation components are processed with a continuous fluid bed process for which no starting cores are required. Typically, all components like the API, pharmaceutical binder(s) and functional ingredients are contained in a liquid - solution, suspension, emulsion or the like - which is fed into the process via spray guns. Particle size is controlled with the help of an online classification system. The MicroPx™ technology is ideally be applied when taste-masked micropellets for the use in oral suspensions, sachets or ODT forms must be provided.

The ProCell™ Technology is a spouted-bed type pelletising process for the preparation of very high concentrated particles; ideally, no additional excipients may be required. For the direct granulation and pelletising process no inert starting beads are required and either, solutions, suspensions, emulsions be processed. The most effect process is achieved when a melt of e.g. pure API is processed, as in this case neither solvents nor excipients are required. With Ibuprofen as a model drug a 100% direct compressable granule can be manufactured.

The innovative fluid bed pelletising technologies complement the actual fluid bed pelletising capabilities: in addition to established pelletising approaches new additional options are made available. A variability of product qualities related with different product throughputs and manufacturing cost are realizable. In particular micropellets being an ideal substrate for taste masked particles for oral suspensions, sachet or ODTs are provided.

Product and process optimization using artificial neural networks – an encapsulation case study

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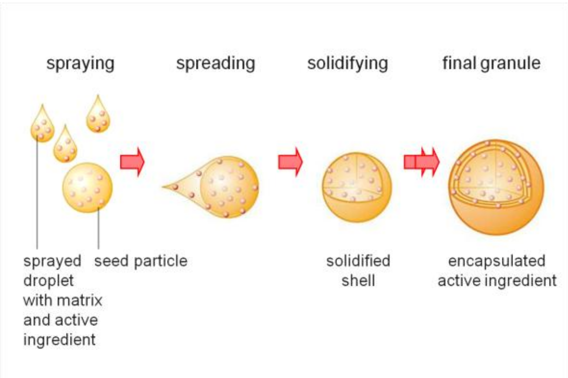
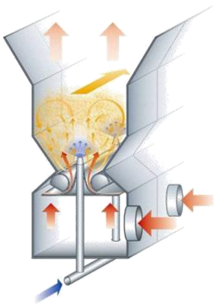
Product and process optimization becomes increased importance in all kind of industry. For instance in food and agricultural industry speciality products must be developed with focus on yield and costs of formulation.

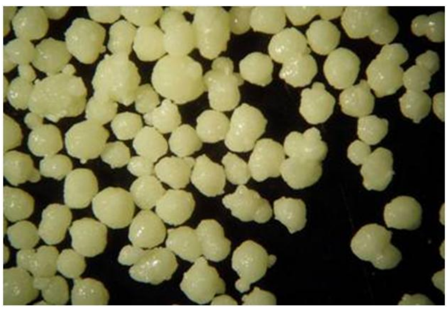
The paper reports a case study involving the encapsulation of volatile components such as flavors, aromatic oils or fragrances to improve their storage stability, to protect these sensitive materials for instance against oxygen or to reduce contamination risks.

A continuous operating spouted bed apparatus was used to carry out the process where a liquid matrix material containing the active ingredient is spray granulated.

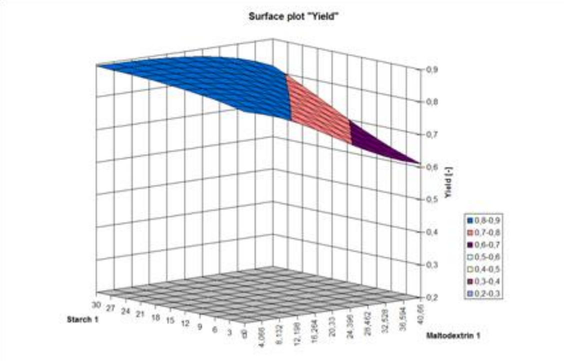


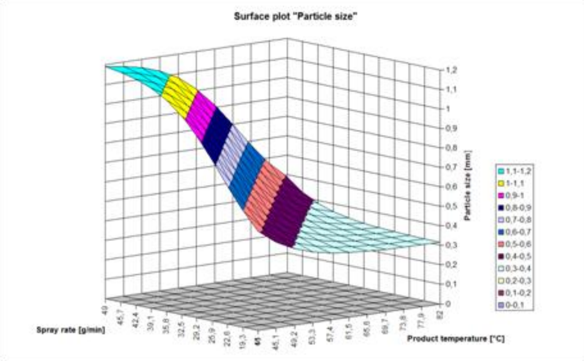
Based on various experiments in laboratory scale on a Glatt ProCell 5 unit a statistical process model was derived based on artificial neural networks. A parameter study and sensitivity analysis was performed to determine the main process conditions and formulation variables.





The multi-dimensional model of the process supported the optimization of product properties (e.g. yield of active ingredient, particle size, particle sphericity …) and related process conditions (e.g. product temperature, spray rate, composition of spray liquid …).





The results show that artificial neural networks can be used as fast and meaningful tools in process and product optimization. Based on the statistical model product properties could be associated with process conditions.

Product driven process synthesis of granulation processes

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Granulation process is a multi-scale process, where micro-scale (inter-particle and binder interaction) and macro-scale (operating conditions) influence final product quality. Similar to Mort et al (2007), we took an intermediate approach between micro and macro scales. We took seasoning cube manufacturing process as an example, where we defined the fundamental tasks which must take place in order to convert inputs (raw materials) into output (a certain microstructure of granules to be compacted in cubical shape). Douglas et al. have successfully used this approach for non-structured products in chemical industries, which they called as Process Synthesis.

In this paper, we followed the product driven process synthesis methodology for redesigning an existing granulation operation of making seasoning cubes. In the existing process scheme, all the dry ingredients are mixed in a high shear granulator, followed by addition of molten binder around the “chopper” blades, which is further mixed and cooled in large bins. Next, this solidified intermediate product is grinded and formed into the final cubes. Starting point for the process synthesis is a characterisation of the seasoning cubes in terms of micro-structure and the inputs, such as raw materials, and their physical characteristics like size, shape etc. In the next step we have defined the fundamental tasks, such as homogeneous binder distribution, mixing, particle growth, air-removal etc. to convert the raw materials to the seasoning cubes. Based on the fundamental tasks alternative process flow sheets have been generated by arranging these tasks in parallel and series combinations. The number of alternatives has been brought down to a workable number by using heuristics. These alternatives have been experimentally tested on the pilot scale.

Our results show that adding the binder differently (spraying over the granulating mass) improves the final product characteristics like homogeneity, flow-ability and tablet-strength. We have also shown that by granulating only the less flowing components in the recipe and adding them back to the rest of the recipe increases the flow-ability of the whole mass substantially. Here the amount of binder remains the same as in the original recipe. Although the resulting mass from the modified process had somewhat higher water activity and the flow-agent was absent, it still had better flow-ability than the standard sample from the standard process with the flow-agent. Good flow-ability is important for the further down-stream process. At the same time, there is flexibility in the formulation space and cost savings due to a reduction of flow-agent. A patent on this new process has been filed.

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Patent application: EP07123107 (pending)

Study of foam-assisted granulation in food model systems

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Granulation is a well-known process commonly used in the pharmaceutical and food industries. In conventional granulation, a liquid binder is added to the powder either in a fluidised-bed granulator or in a mixer granulator via a spray nozzle, in order to divide the liquid finely right from the start. Subsequently the particles are bound by the droplets via capillary bridges. In foam-assisted granulation, developed empirically in the pharmaceutical industry, the binding liquid is added as an aqueous foam. Claimed benefits are the elimination of nozzles, improved process robustness in manufacturing and shorter drying time, resulting in a reduction in granulation manufacturing costs. To develop a potential application for foam granulation, especially in food industry, it is necessary to understand how the processing conditions, such as impeller speeds in high shear granulation etc., affect the granulation performance by foamed binder.

In this study, effects of formulation, foam properties and process parameters (impeller speed, mixing time, and chopper speed etc.) on a foam-assisted high-shear granulation process have been studied in two food model systems. The granule structures were evaluated by SEM, and the granulation yield was used to quantify the granulation performance. The results show that the granulation by foamed aqueous binder simplifies the granulation process, giving higher granulation efficiency compared to the traditional spraying process. Granule structure and properties (density, porosity, and attrition) from foam-assisted granulation did not strongly depend on the process conditions. Concentration of binder in the foam affected the granulation significantly at low level, while levelling off at higher concentration. A porous structure was observed for certain process conditions, which is quite critical for the application in food industry. Increase of the amount of foam lead to better granulation efficiency for both systems. By using the foamed aqueous binder, less water and binder were needed in both systems studied.

Improving liquid distribution by reducing dimensionless spray flux in wet granulation – a pharmaceutical manufacturing case study

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Controlling liquid distribution in a wet granulation process is critical to maintaining control of both nucleation and growth, as highly-saturated patches created by uneven liquid distribution will have a much higher growth rate and may form large “balls”. The size of these balls depends on the granulator scale, but in full scale pharmaceutical manufacturing these lumps are commonly 0.5-1 inch in diameter, but may even be larger. The presence of a significant quantity of “balls” frequently results in downstream problems in drying, milling, compression and final product attributes.

This paper presents a case study of attempting to improve the liquid distribution during manufacturing of an existing wet-granulated product with a long history of “balls”. The flowrate and spray area of the original nozzle were measured, and a simple estimation of the drop size was obtained by a high-speed photograph and image analysis. The powder surface velocity in a 400L Diosna was measured using a high speed camera and a simple image analysis technique for several batches using different lots of the drug. Since the manufacturing process was validated and filed, the only change that could be made to attempt to reduce the spray flux and improve liquid distribution was to find a new nozzle. A new nozzle was selected and implemented in a full-scale production batch and the results are compared with the original nozzle conditions. Reducing spray flux by changing the nozzle actually increased ball formation, contrary to what was expected. For products in the growth and/or induction regimes, *increasing the efficiency of liquid distribution may mean that less total liquid is required to be added to achieve the same extent of granulation*. Improving liquid distribution without also reducing the total volume will result in a shorter induction

period and/or a higher growth rate and larger granule size. The study found that the *major contribution to batch-to-batch variation in spray flux was the large variations in powder surface velocity for each batch*, which is presumably caused by changes in the physical properties of each lot of drug. This has not been reported previously and has important implications for understanding the causes of variability in liquid distribution and granule/ball size in full-scale production of wet granulated pharmaceutical products.

Effect of formulation hydrophobicity on drug distribution in wet granulation

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Wet granulation is a process of enhancing the powder properties by producing larger particles from the agglomeration of agitated fine particles with liquid. The production of enlarged particles or "granules" is often carried out in high-shear granulators, an equipment item prevalent in the pharmaceutical and food industries. In the pharmaceutical industry, the wettability properties of the formulation are important to produce strong granules with a narrow size distribution. However, the use of hydrophobic drugs in the formulation poses problems in granulation which are often overcome by the use of surfactants; but this may not always be possible. Conventional wet granulation theory focuses on the granulation of predominantly hydrophilic formulations. Some works on hydrophobic granulation (Aulton and Banks, year) have found that as the hydrophobicity of the formulation increases, the average size of the granules decreases. However an explanation for the decrease in granule size has not been proposed, which may be influenced by the lower proportion of hydrophilic component available for granulation. The observation and reasoning behind the granulation behaviour for a mixture of hydrophilic and hydrophobic powder forms the basis of this paper.

Granulation experiments are carried out on varying degrees of formulation hydrophobicity and the granulation batch is sieved into different size fractions. Sieve fraction assays are then completed for each size fraction, to determine the average granule composition and the distribution of hydrophobic drug. The effects of formulation hydrophobicity on the drug distribution of granules and average granule size will be discussed.

Producing hollow granules from hydrophobic powders in high-shear mixer granulators

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The formation of hollow granules from hydrophobic powders in a high-shear mixer granulator has been investigated by changing the binder/ powder mass ratio and studying the effects on granule size and structure.

In this study, a mixer granulator was filled with 100 grams of hydrophobic fumed silica and then varying quantities of 5% Hydroxy Propyl Celloluse solution was slowly sprayed into granulator. The range of binder to powder ratios varies from 1:1 to 15:1. Granules were then dried at 60 º C in a fan forced oven.

This paper compares the particle size distributions, scanning electron microscopy (SEM) images and x-ray tomography (XRT) images for different binder/ powder mass ratios. The results show that the granule mean size grows and the fraction of ungranulated (fine) particles decreases as the binder/ powder mass ratio increases. Simultaneously, the morphology and structure of the hollow granules changed from spherical to a deformed structure.

Keyword: Hollow granule, liquid marbles, granule structure, hydrophobic powders, SEM, XRT, fumed silica.

Rewetting effects and droplet motion in wet granulation

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Wet granulation is a process where assemblies of particles are formed to make a "granular mass" with improved flow, reduced dust and improved powder safety. For granulation processes in the high shear mixer, the powder is agitated in a vessel while liquid is sprayed onto the powder. The initial drops form "nuclei" granules which can be predicted using a nucleation regime map. However, this approach assumes that only dry powder enters the spray zone. Industrial granulation processes commonly add 20-50 wt% fluid, and the partially wetted powder recirculates many times through the spray zone. The effect of partially wetted powder re-entering the spray zone is not currently known.

To investigate, single drop nucleation experiments were carried out at controlled separation distances. A strong correlation between drop penetration time and lateral droplet motion on the powder bed surface was observed. For fast penetrating systems, nucleation was only slightly affected by the presence of the previous droplet. However, systems with long penetration times showed lateral droplet motion due to Laplace pressure differences. Consequently there is a wider distribution of size and nuclei saturation than is anticipated by the dimensionless spray flux. Therefore the droplet migration behaviour implies that the drop controlled regime boundary should be adjusted to become a function of the drop penetration time; a lower spray flux is required to remain in the drop controlled regime as the penetration time increases.

Single foam in high shear granulator

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Foam granulation is a new approach to wet granulation process, where foaming binder solution is used to granulate the powder particles. This paper studies the behaviour of foams on a dynamic powder bed in a high shear mixer by filming single foams of fluids with various foam qualities as they penetrated into moving powder beds in a high shear mixer.

At different impeller speed, two critical powder flow patterns are observed in a mixer granulator: bumping and roping flows, as previously reported by Litster and coworkers (2002). Under bumping flow, foam dispersed on a moving powder bed was observed to remain visible on the powder surface for at least 10 seconds depending on the foam properties and elongate during the powder rotating motion. Under roping flow, foam moved towards the centre of the granulator bowl within 1 second of mixing and was well dispersed by mechanical mixing.

The interactions of foam quality and the powder flow pattern are discussed and two distinct regimes are proposed: 1) Under bumping flow, a wet foam tends to induce local wetting and nucleation. Foam drainage and decay properties dominate in this regime 2) Under roping flow, regardless of foam quality, foam will be dispersed by agitated powder flow. This regime is mechanical dispersion controlled. These two regimes imply that two different foam wetting and nucleation mechanisms are involved in foam granulation.

Effect of physico-chemical properties and process variables on high shear mixer granulation: characterization, kinetics and scale-up

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In this study wet granulation of a cohesive microcrystalline cellulose powder (Avicel 105, $d_{3,2}$=11μm) has been investigated on a Mi-Pro® high shear granulator with bowl sizes of 250, 500, 900 and 1900ml and a Zanchetta Roto Junior® 10l planetary high shear granulator. As binder ultra-pure water as well as solutions of HPMC and PVP were used. The effect of impeller speed on granule size and porosity has been studied and correlations with different dimensionless numbers and scale-up rules, like impeller tip speed, Froude number and Stokes deformation number have been made. Granule strength was investigated with regards to the binders used in our experiments. The observed growth mechanism (Figure 1) allowed us to define three characteristic granule size fractions: fines, intermediates and coarse. Torque curves recorded during granulation on the Mi-Pro are found able to ensure reliable process control at all scales. Water liquid requirement is found to vary only slightly with changing impeller speeds. Observations made in this study will serve to evaluate population balance equations. This study aims to show the effect of physico-chemical properties, process variables and geometry on high shear mixer granulation.

Keywords: wet granulation, high shear mixer, impeller speed, viscosity, scale-up, torque curves

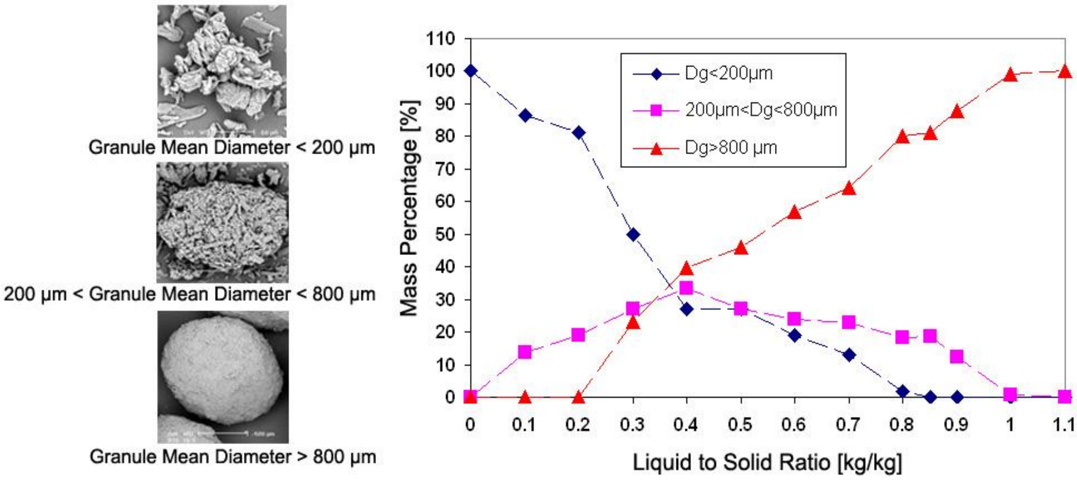

Figure 1. Evolution of fines, intermediates and coarse granules mass percentage in the Mi-Pro® as a function of Liquid to Solid Ratio with a 900 ml bowl, impeller speed of 460 rpm and chopper rotation speed of 3000 rpm

Modelling and control of pharmaceutical granule milling in a conical screening mill (Comil)

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Conical screening mills, specifically Comils, are ubiquitous in the secondary manufacture of solid oral dosage forms in the pharmaceutical industry. Comils are used for purposes ranging from coarse delumping to fine control of granule size. Control of granule size is important, in particular with respect to manufacturability (flow) and product quality (weight uniformity, dissolution). In addition, granule size can be linked with other tablet physical attributes such as hardness. Population balance models are ideally suited to mechanistically modelling the change in the granule size distribution as the result of granule breakage. Use of a population balance model for granule breakage requires identifying a suitable breakage rate constant and a breakage function (or fragment size distribution). A method is presented whereby assuming limited hold-up time the model can be made independent of the breakage rate, leaving the breakage function to be determined. This can be achieved by fitting the breakage function in the population balance model to experimental measurements of granule size distributions before and after milling. Correlation of the breakage parameters with experimental conditions can give insight into granule mechanical strength as a function of upstream processing conditions. Establishing the breakage parameters for a given process train, can be used to identify and control suitable mill operating parameters to ensure a target granule size is achieved.

Granulation of gelling polymers with foamed binder solutions

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The most common way of granulating powders is by addition of liquid binder under agitation to ensure coalescence and growth of the primary particles. For granulation of gelling polymer powders a uniform distribution of granulation liquid is especially important. The need to reduce local overwetting in the powder mass is obvious to prevent instant gelling and lump formation. Traditional techniques of binder addition such as use of spray nozzles are far from optimal especially in large production scale. A suggested improvement is the addition of liquid binder as foam. Foamed binder solutions with a high gas-to-liquid ratio show a huge surface area, which will improve liquid distribution.

The purpose of this study was to compare foam and water as a granulation liquid in a high-shear wet granulation of a gelling polymer. Hydroxypropyl methylcellulose (HPMC) K4M (Dow Chemicals) was used as a gelling polymer. For liquid binder granulations pure water was used as a binder liquid. For foamed binder granulation a solution consisting of 1500 ml 2% HPMC K4M and 500 ml 0.1 % HPMC E3 was prepared to generate the foam. Foam was generated via the DOW foam generator using air pressure. A plastic tub fed the foam into the granulation vessel. The foam quality was always >95%. Granulations were carried out with Mi-Pro (ProCepT, Zelzate, Belgium) using a 1.9 l bowl, dry powder mass 125 g, impeller speed 500 rpm and chopper speed 1500 rpm. Liquid/foam amount used varied from 0.1 to 0.8 g/g. Process data (power consumption) was collected during granulations. Wet granule properties (wet bulk density, consistency, at-line NIR spectra and magnetic resonance imaging (MRI)), dry granule properties (particle size distribution, bulk and tapped densities) and tablet hardness were investigated.

NMR imaging was used to measure the state of water. The liquid binder granules had a slower T2 relaxation rate than foamed binder granules, slower decay to the baseline determined by the signal/noise ratio in the experiment, which indicated that granules produced by liquid binder addition had more free water after granulation while granules produced by foamed binder addition have more water in a bound state.

At low liquid amounts (0.1 g/g and 0.3 g/g) the granules were very fluffy and resulted in poor flowability independent on method of binder liquid addition. However, at 0.5 g/g the foamed binder granulation yielded freely flowing granules, while the liquid binder granulation yielded poorly flowing granules. The particle size of foamed binder granules was coarser than liquid binder granules before milling but after milling the particle size distributions were almost identical. Granule growth without excessive densification gave good tableting properties for foam granulations.

The results show that foamed binders enabled an excellent distribution of granulation liquid and an efficient granule growth in gelling polymer powders. The slightly different mechanism of granule growth resulted in large and soft granules, improved granulation yield and flowability and good tableting properties. DOW´s Foam Technology appeared to provide a tool to be able to develop robust wet granulation processes.

Roller compaction process modeling: prediction of operating space

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Roller compaction is an important granulation unit operation in the production of pharmaceutical tablets. It offers an effective processing route for moisture and heat sensitive active compounds, and the continuous aspect facilitates scale-up and manufacturing on-demand. Development of a robust formulation and process for a new drug product is challenging, due to limited supply and variable physical properties. Formulation and process development is often undertaken experimentally, using statistical experimental design methodologies. These approaches allow rapid identification of key relationships and interactions between operating parameters and intermediate and product attributes. However, the underlying fundamental physical relationships are often not established, making it difficult to predict the influence of a change of input material properties, or a change of scale. Johanson developed a theory for the pressure distribution between the rolls in a roller compactor using powder mechanics. In more recent work, instrumented roller presses have been used to validate the model. The model allows blend characterisation data, specifically compression and flow properties, to be used to predict the behaviour of the roller compactor. The blend characterisation can be performed on very small quantities of material, allowing calculation of appropriate operating conditions for the roller compactor, negating the need for large scoping experimental designs. In this paper comparison is made between conventional statistical experimental design analysis and powder mechanics predictions for the optimum operating space for a drug product.

Breakage of drop nucleated granules in a breakage only high shear mixer

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High shear mixer granulators are used in a variety of processes, including the pharmaceutical, food and detergent industries. Despite the important role wet granule breakage plays in high shear granulators, the mechanism of breakage within the granulator is poorly understood. In order to effectively scale-up and model the granulation process, it is necessary to study the granule breakage mechanism.

This paper examines the effect of equipment parameters on the breakage of drop-nucleated test granules in a novel "Breakage Only Granulator", designed to isolate the breakage mechanism from other mechanisms of granulation. The Breakage Only Granulator is a modified high shear mixer with interchangeable impeller blades. A powder bed of sticky sand (sand coated with 0.1 Pa.s Silicone oil) was used as the flow medium. Two impellers were used in the Breakage Only Granulator experiments; the 11º bevelled blade was designed to give a mixture of shear and impact forces in the granulator, and the frictional flat plate impeller was used to minimize impact and maximize shear in the granulator.

Pre-formed drop-nucleated test granules were placed on the sand bed and mixed for 15 s at speeds of 500 and 750 rpm, then sieved to recover the surviving granules and granule fragments. The breakage fraction of granules (the fraction of original granules which broke) was then compared to the peak flow stress of pellets of the same formulation, measured in earlier work.

Significant breakage occurred in experiments using the bevelled blade impeller. The amount of breakage decreased with increasing peak flow stress, with some considerable scatter in the results. There was considerably more granule breakage at 750 rpm impeller speed than at 500 rpm, emphasising the importance of impeller speed in the granulator.

The frictional flat plate impeller at 500 rpm showed very little breakage for all formulations. At 750 rpm, only the weakest formulation showed considerable breakage. These results emphasise the profound effect of impeller geometry on the breakage process and suggest that impact is the primary cause of granule breakage in high shear mixer granulators.

Diametrical compression of wet granular materials

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While significant advances have been made in the study of granule nucleation and growth, breakage remains poorly understood. Despite this, wet granule breakage can be a significant mechanism in granulation, particularly in high shear granulation, which is frequently used in the pharmaceutical, detergent and food industries. In order to understand and model the granulation process, it is necessary to study the granule breakage mechanism.

This paper focuses on characterizing the deformation of single wet granular pellets under diametrical compression. Cylindrical pellets (20 mm diameter, 10 mm height) of granular material were compressed diametrically in an Instron DynaMight™ load frame at velocities ranging from 0.1 to 180 mm/s. Three sieve fractions of glass ballotini and two fractions of lactose powder were used to vary particle size and shape. Four binders were used to vary binder viscosity: water, lactose solution (for use with lactose formulations only), 1 Pa.s Silicone oil and 30 Pa.s Silicone oil.

Pellet compression was filmed using fast frame video to capture pellet deformation with time, and link stress-strain curves with breakage behaviour. The geometry of these pellets suited the study of granule deformation and mode of failure.

Two modes of granule failure were observed: semi-brittle, and plastic. Semi-brittle breakage behaviour was characterised by a catastrophic crack propagating through the centre of the pellet, with some small plastic deformation at the platens. Pellets deforming by classic plastic deformation showed no major crack, and flowed between the platens like a paste. Pellets that displayed diagonal cracking or micro-cracking at high strain were classified as plastic.

Criteria were developed to distinguish between plastic and semi-brittle pellets. Pellets with a peak stress value at a strain less than 5 % were classified as brittle; pellets with a peak stress value at a strain above 5 % were classified as plastic.

Plasticity increased with increasing strain rate and viscosity, however the clear Capillary number transition demonstrated in earlier work using compression in axial geometry did not apply to these results. Non-spherical particles showed semi-brittle fracture at much lower values of Ca. It is likely that the failure mode is determined by a balance between inter-particle friction and viscous liquid dissipation.

Construction of a quality index for granules produced by fluid bed technology by application of the correspondence analysis as a discriminant procedure

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The production of granules by wet granulation in a fluidized bed was assessed after the construction of a quality index based on a file of attributes (relevant factors). These attributes are combined by a methodology relying on Correspondence Analysis, as a discriminant procedure, using two extreme simulated active vectors (Pereira, 1988, Pereira *et al*., 1993), representing, respectively, the best and the worst case for the granules quality output ("bad" and "good" pole). From those a single continuous synthetic variable – the quality index – can be produced referring to a more significant set of samples.

As an example of the methodology the work compares the quality of granules produced at a laboratory scale and a pilot scale. The factors contribution to the bad or good pole allowed the identification of the most relevant factors that affect the quality of the granules. The factors studied, according to a center of gravity design, included formulation (solubility of a drug, different grades of polyvinylpirrolidone, the polarity of the granulation solution) and processing factors (the rate of administration of the granulation solution, the atomizing air pressure and the fluidizing air rate). Granules were evaluated for production yield, drug content, size, densities (true, bulk and tapped), friability, flowability and compressibility (Dias and Pinto, 2001). The study has emphasized the differences between the laboratory and pilot scales and the relative importance of each factor for the quality of the granules produced.

Keywords: Correspondence Analysis, Fluid bed, Granulation, Quality Index

An engineering analysis of the spheronisation process

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Extrusion-spheronisation has been traditionally used in the pharmaceutical industry for controlled release drug delivery. Extrusion-spheronisation is important as a continuous granulation method. The process involves creating a wet mass, extrusion, and spheronisation. The preparation of the wet mass (which is similar to wet granulation) and extrusion (used in a wide range of industries) have been extensively studied and are relatively well known. The least understood process is spheronisation, which involves breaking the extrudates down to small roads, which are the rounded to form spherical particles.

Research into spheronisation is limited to large scale experimental studies where the material composition, liquid content and the parameters of the process are varied until an acceptable product is obtained. In our approach we start from specifying the required properties of the final granule (quantified in terms of physical and mechanical properties). Then the preceding operations designed step by step backwards ending with the selection of initial powder composition, liquid content and specifying the mixing process and extrusion equipment.

In this paper we concentrate on the spheronisation process. Finite element analysis is employed to examine in detail the process of transformation of a cylindrical rod into a sphere through successive impacts. The model variables include physical and mechanical properties for the rod, impact velocity and details of contact interactions, which are calibrated using standard materials testing methods. The model predictions are validated using high speed video observations of the spheronisation process. An operating spehronisation window is determined and it is shown how the results can be used for selecting and specifying the processes preceding spheronisation.

Batch top-spray fluid bed coating: scale-up insight using dynamic heat- and mass-transfer modelling

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In the chemical and pharmaceutical industry sensitive active solid products, such as enzyme containing granules, are often produced by coating the active ingredient onto inactive filler cores in fluid beds. The desired product thereby consists of unagglomerated individual carrier particles each coated homogeneously with a layer of the active ingredient. Besides being able to maintain and protect the activity of the active ingredient, process optimisation often goes in the direction of finding correct formulation and process conditions in order to balance between excessive agglomeration and excessive spray drying of the feed.

In industry, product and process properties are typically optimised in small- and medium-scale pilot fluid beds and then transferred to production-scale. The scale-up of a fluid bed granulation process requires decisions to be made at many levels, including: fixed parameters (e.g. nozzle and fluidisation chamber dimensions), parameters related to the core material (such as price, composition, porosity, sphericity and more), coating solution (e.g. viscosity, work of adhesion and more) and the type of fluid bed, input parameters, operating conditions including spraying and fluidisation conditions as well as processing time etc. With such a variety of interlinked parameters and properties, combined with a general lack of quantitative understanding of the granulation process, it is obvious that scale-up of a fluid bed granulation process is a challenging task.

In the present work a mathematical model for batch top-spray fluid bed coating processes presented in [1] was modified for the present study. The model is based on one-dimensional discretisation of the fluid bed into a number of well-mixed control volumes. In each control volume, dynamic heat and mass balances were set up allowing the simulation of the contents of water vapour, water on core particles and deposited coating mass as well as fluidisation gas, particle and chamber wall temperature. The model was used to test different scale-up principles by comparing simulation results with experimental temperature and humidity data obtained from inorganic salt coating of placebo cores in three pilot fluid bed scales being a 0.5 kg small-scale (GEA Aeromatic-Fielder Strea-1), 4 kg medium-scale (GEA Niro MP-1) and 24 kg large-scale (GEA MP-2/3). Results show good agreement between simulated and experimental outlet fluidisation air temperature and humidity as well as bed temperature. Simulations reveal that vertical temperature and humidity gradients increase significantly with increasing scale and that in fluid beds as the simulated 900 kg (RICA-TEC Anhydro) production-scale, the gradients become too large to use the simple combined Drying Force/Relative Droplet size scale-up approach presented in [2] without also increasing the inlet fluidisation air temperature significantly. Instead, scale-up in terms of combinations of the viscous Stokes theory with simulated particle liquid layer profiles (obtained with the model) is suggested. In this way, the given fluid bed scale may be optimised in terms of low agglomeration tendency for a given process intensity across scale.

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Characterization of coating formulation and process manufacturing understanding as tool for determination of coating's strength

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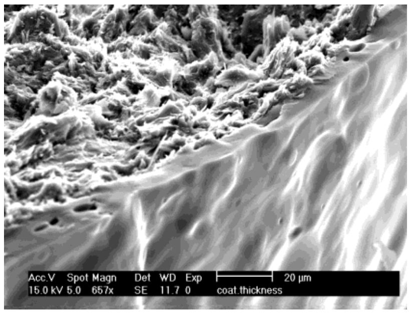
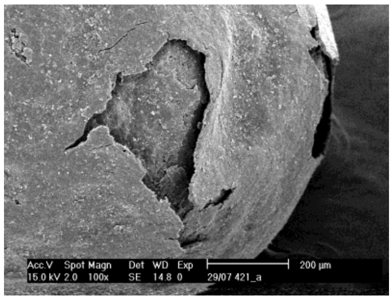


When we apply a coating onto a particle we need to guarantee that the product has sufficient chemical stability and physical strength to survive the thermal, mechanical and humidity stresses encountered during manufacture, packaging, distribution, storage, and use. The design of a commercial manufacturing process that meet all of these requirements require the careful characterization of the coating formulation, and the development of in depth understanding of how its properties impact the ultimate performance of the drug product.
This is the basis for many ongoing "quality-by-design" initiatives in both pharmaceutical and Food industry that are intended to:

- Increase the efficiency of manufacturing processes and reduce materials and money wastes,
- To develop both a product which is designed to meet customer's needs and performance requirements,
- To develop process which is designed to consistently meet product critical quality attributes.

Thus a "quality by design" approach will then result in an in-depth understanding of the interactions of the several variables such as coating–carrier raw materials (Density, Molecular Weight, Glass Transition), coating solution (Viscosity, Surface Tension), manufacturing (Process Used, Process Variables) and environmental conditions (Storage Temperature and RH), etc. and facilitate manufacturing of a coated particle. The general aim of this is to obtain the desired quality-functionality of the coating starting from the complete knowledge of the coating polymer. With these ideas in mind, we use both a different investigation criteria and a completely new setup fluid bed coating experiments, which encompass the advantages of the afore-mentioned approach.

The idea underlying our new setup is simple: controlling and recording all the relevant variables (Fluid Bed Temperature first of all before-during-after a single experiment, Inlet Air flow rate and temperature, Coating Solution spraying rate…) we can directly relate end-product performance, manufacturing parameters and storage conditions. Factorial Design approach has been used to estimate the overall main factor effects and the interaction between different variables.



Characterization of coated particles by means of Repeated Impact Tester and Nano-Indentation, the accurate analysis of the morphology of the structure by SEM and AFM and the assessment of coating raw material's properties (done by means of up-to-date techniques) provides us the ability necessary to design manufacturing processes that optimize the desired performance properties.

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Stability of sub micron grinded food products

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The objective of this work was double: first to achieve grinding organic crystalline food compounds to sub-micron scale and second to investigate the new characteristics such as efficacy and stability of the product. The ball mill used was a Dynomill and the grinding media consisted of zirconium oxide beads. The grinded powder was a poorly water soluble product. Laser diffraction techniques were used to analyze the particle size distributions. During grinding the average particle diameter of a particulate product is reduced to a minimum value in the submicron range.

The stability against agglomeration of the grinded particles is dependent on the pH of the suspension and the presence of additives such as surfactants or viscosity enhancers.

The agglomeration of the particles has been determined with a method making use of modelling of the sedimentation profile of the particles using the Stokes equation.

The agglomeration behaviour of particles at different pH is then explained by the determination of the zeta potential. The closer the pH to the isoelectric condition, the less repulsion between the particles and thus the more agglomeration is occurring.

Compaction of re-crystallised ibuprofen

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Ibuprofen is a commonly used non-steroidal anti-inflammatory drug, normally formulated and produced as tablets. However, ibuprofen is known to display poor compaction properties and exhibits punch adhesion during tablet manufacture. The aim was to recrystallise ibuprofen from a range of solvents, assess particle morphology and compaction properties.

Ibuprofen 20 (Albermarle, USA) was recrystallised from a range of solvents in batch experiments. Crystallisation was initiated by cooling of a saturated solution with constant stirring and the product harvested by Buchner filtration. Samples were evaluated for the habit modifying influence of the solvent using optical (Olympus BH-2) and scanning electron microscopy (FEI Quanta 200). The morphologies observed ranged from equidimensional blocks (methanol) through plates (isopropanol) to elongated rods (cyclohexane). Crystallinity of samples was confirmed by powder X-ray diffraction using a Rigaku Miniflex. Melting points and heats of melting were determined by differential scanning calorimetry (Pyris 1 DSC, Perkin Elmer, USA) and in all cases showed no detectable difference to the control. The tapped density and flow ability (Carr's index) of each powder was determined.The compaction properties of the re-crystallised ibuprofen and control samples were assessed using a Stylcam® 100R rotary press simulator (Medel'Pharm, France) fitted with 11.28 mm flat-faced tooling. The effect of compaction force (5 or 25 kN) and speed (5 or 25 tablets min^{-1}) on tablet tensile strength was evaluated. Compaction energies (plastic and elastic) were measured via the Analis® software (v. 2.01, Medel'Pharm, France). Additionally, the re-crystallised ibuprofen and control samples were individually blended with an equal amount of lactose (Tablettose® 80, Meggle, Germany) in a turbula mixer (Type 2B, WAB, Switzerland) for 5 min before being passed through a 500 μm aperture sieve (Endecotts, UK). Each mixture was then lubricated by adding 0.5 %w/w of magnesium stearate (BDH, UK) and mixing for a further 2 min. Tablets of each ibuprofen-lactose blend were produced under the same conditions as described for the individual ibuprofen samples and adhesion of ibuprofen to the upper punch was assessed as previously described by Roberts et al (2004).

Re-crystallised ibuprofen samples were found to have improved flowability and equal or better tablet strength than the control. Ibuprofen recrystallised from 2-ethoxy ethyl acetate also displayed lower levels of elastic energy during compaction. Additionally, when formulated with lactose, recrystallised ibuprofen samples displayed lower punch adhesion levels and improved tablet strength compared to the control, particularly at a low compaction force. Our results indicate that ibuprofen re-crystallised from various solvents can offer advantages in terms of particle morphology, flowability and compaction properties. Additionally, a reduction in punch adhesion may also be attained thus aiding tablet manufacture.

Roberts, M., Ford, J.L., MacLeod, G.S., Fell, J.T., Smith, G.W., Rowe, P.H., Dyas, A.M. (2004) *J. Pharm. Pharmacol.* **56** 299-305.

Conceptual design of a pseudo-continuous granulator-dryer

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The term "conceptual design" is a well-established concept in the chemical industry as far as large scale and continuous processes are concerned. Conversely, there is not a clearly outlined approach to conceptual design for pharmaceutical process. The seminal work of Douglas (1988) paved the road for an advanced design technique to study the feasibility and profitability of continuous processes. This manuscript tries to apply the same concepts, logic, and way of reasoning to the granulation and drying processes performed by a pseudo-continuous unit. First of all the paper describes the physical structure of the equipment while identifying the main unit operations that it performs sequentially. Afterwards, we identify and discuss the most ticklish unit operations in order to determine the critical operative size over which the process departs from the ideal conditions. Actually, both experimental and industrial evidences have repeatedly shown that over a certain amount of processed powder, the product quality is not ideal if compared to small batch quantities of the same ingredients.

This is probably due to the mixing, the kneading, and the drying that cannot be run under ideal process conditions. The idea is to reduce the size of a single batch while reducing the batch time. The result is a device that is rather different from common granulators and dryers and that allows avoiding any scale up problems.
The scale reduction allows achieving almost ideal process conditions as well as improving the quality by design notion, which is strongly recommended by the FDA and the local regulatory authorities. As far as the scale up problem is concerned, the

manuscript will show how it is possible to fine tune the process operative conditions for a Phase I equipment and to retain its dimensions and nominal operation while passing to the Phase II and finally to the Phase III experimentation. Also under conventional industrial conditions, the same process unit is kept in place, the solution being a suitable number of single devices coupled and operating in parallel.
The implementation of a number of parallel units, whose batch duration is of one and even two orders of magnitude shorter, gives rise to the pseudo-continuous concept. Actually, each single unit is still working as a batch device but the resulting equipment is an almost continuous (*i.e.* pseudo-continuous) process unit. A further achievement of the small-scale device, which is the single element of the whole equipment, is the real time release of the product. By tracking the process dynamics and the corresponding quality indicators it is possible to assess the quality of the final product in real time. If the product does not satisfy the quality paradigm, it is then possible to reject the single batch, whose quantity is rather negligible if compared to the conventional, large-scale, process units. This means lower reject quantities, higher economic revenues, and possible removal of the *a posteriori* quality control of the product.

Dynamic binder liquid distribution in a high shear mixer granulation process

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In the wet granulation process, binder liquid distribution is known to be a key parameter to control granulation rates and the final granules properties. However in literature, very few studies tackled this problem and the dynamic of the liquid distribution is still not very well understood, especially in high shear mixers. The few published studies are more concerned with liquid re-distribution after the complete addition of the binding agent.

In this study, we are especially interested in characterizing the time evolution of granules properties during binder liquid addition. The following three properties have been followed: the size distribution, the porosity of several size classes and the binder liquid content of the granules. The effects of three operating parameters have been studied: the impeller rotation speed, the binder flow rate and the water content of the binding liquid (mixture of water and isopropanol).

Granulation experiments are carried out in a 0.5 L high shear mixer Mi-Pro (Pro-C-epT, Zelzate, Belgium) using lactose and polyvinylpyrrolidone powders as pharmaceutical excipients. In order to follow the binder distribution kinetics during granulation process, an original tracing method has been developed. Nigrosine dye is used as tracer of the binding liquid. After drying at ambient temperature, granules are sieved into 12 classes and dye content is analysed in each granule diameter class by spectrophotometry after complete dissolution.

We notice that the binding liquid is highly heterogeneously distributed in the particles population until a homogeneous state is obtained, characterised by an equal binding liquid amount in each diameter class. The time required to reach this homogenous state is variable depending on the operating conditions.

In addition, it clearly appears that as long as the tracer is heterogeneously distributed in the particles population, the larger the granules the higher the binder content per granules mass unit.

The results also show that granules growth rate appears to be mainly dependent on binding liquid flow rate and slightly influenced by impeller speed.
A kinetics model is proposed to describe binder liquid transfer among different granule classes. Transfer rate constants are calculated and it is deduced that the main effect is due to the binding liquid composition. However, it is difficult to discuss the viscosity and the superficial tension influence since these two parameters vary simultaneously. We also show that increasing the impeller rate induces a slight increase of the transfer rate whatever the binding liquid flow rate. Finally this transfer rate can be related to the median diameter of particles: d_{50} increases with transfer rate when water is used as binding liquid and there is no d_{50} variation when the binding liquid is a mixture of water and isopropanol.

Modelling particle size distribution and binder liquid distribution in wet granulation by population balance

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Population balance equation is an usual tool to model granulation process and is often used to simulate particle size distribution evolution against time. In this study the particle size distribution and binder liquid distribution were measured all along the granulation process and the population balance equations have been extended to describe granulation according to the binder distribution in particles.

Granulation experiments were carried out in a 0.5 L high shear mixer Mi-Pro (Pro-C-epT, Zelzate, Belgium) using lactose and polyvinylpyrrolidone powders as pharmaceutical excipients. In order to measure the evolution of the size and binder concentration, granulation was stopped at six different defined times. Granules were sieved into 12 classes and binder content was analysed in each granule diameter class.

The population balance equation was first used to describe particle size distributions evolution during the granulation process. The following equation was discretized and solved using the Kumar and Ramkrishna method.

$$\frac{\partial n(v_i,t)}{\partial t} = \frac{1}{2}\int_0^{v_i} \beta(v_j, v_i - v_j)\, n(v_j,t)\, n(v_i - v_j,t)\, dv_j - \int_0^{\infty} \beta(v_j,v_i)\, n(v_j,t)\, n(v_i,t)\, dv_j$$

Usual kernels have been tested : constant, sum, EKE, ETM and Smoluchowski’s. The best granulation description has been obtained with the product kernel which is the only able to take into account the largest particles evolution. The agreement between experimental and calculated mean number or volume diameter are very good.

In a second part, the binder liquid distribution was also taken into account in the granulation kernel and the mass balance equation has been added, discretized and solved according to an original method, close to that proposed by Kumar and Ramkrishna :

$$\frac{\partial M(v_i,t)}{\partial t} = \int_0^{v_i} \beta(v_i - v_j, v_j)\, n(v_j,t)\, M(v_i - v_j, t)\, dv_j - \int_0^{\infty} \beta(v_i,v_j)\, M(v_i,t)\, n(v_j,t)\, dv_j$$

where $M(v_i,t)$ is the total mass of binder in particle of volume v_i at time t.

The coupled equations allow the prediction of the particle size evolution against granulation time and the simulation of the binder liquid composition in granule which varies against time and particle size.

However, very few kernels depending on the binder distribution are available in literature and none of the most used could suitably describe the granulation process. Particularly, Darelius assume that the granules are saturated in binder which is not the case here. Original kernels have then been proposed, but the binder repartition during its addition needs to be clearly defined to improve the granulation process description.

Dynamic torque measurement in twin screw extrusion process

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The extrusion process has been established in manufacturing of solid dosage forms for many years. One example is the preparation of beads by wet extrusion / spheronization in order to obtain granules with spherical shape and narrow size distribution. The key parameter in this process is the amount of water in the formulation, which correlates with the power consumption of the extruder and determines the granule properties. The dynamic torque measurement can be used to perform an inline monitoring of the energy uptake during granulation process.

The lab scale extruder Micro 27GL-28D (Leistritz, Nuremberg, Germany) was equipped with a torque-gauge (T22, HBM Messtechnik, Darmstadt, Germany) for measuring the mechanical power consumption. The torque-sensor was installed between the motor and the transmission system. Two bellow sealed couplers were used to minimize the effects of tilts between the sensor, motor and transmission (fig.1). The signal was processed by an analog/digital-transformer-card (PCI-6031-E, National Instruments, Los Angeles, USA) within a personal computer. The calibration was done with a lever-mass-system with 9 different masses up to 2.5 kg (resulting in approx. 0-25 Nm). The effective lever was 1.00 m.

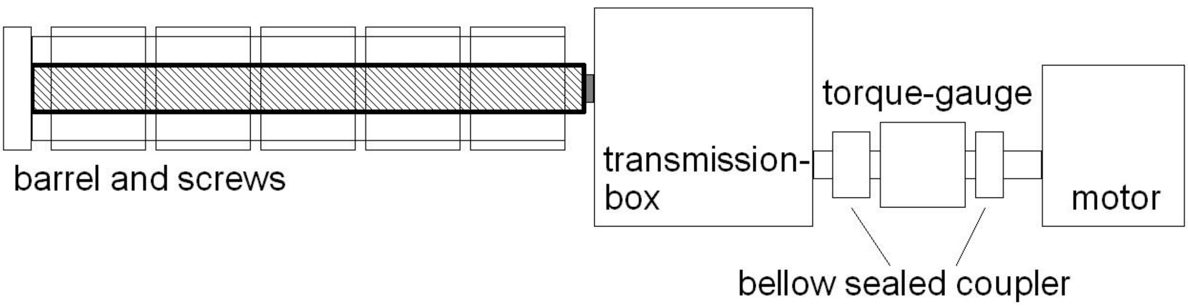

Figure 2: Torque-gauge in the Leistritz Micro 27GL-28D

The measuring system was validated in accordance to the ICH-Guideline:

- The precision was calculated for several measurements as coefficient of variation between 0.29 and 0.54 %.
- The accuracy was proven by using weights as basic unit.
- The limit of quantification was found at 0.23 Nm and a responsivity of 0.0184 V/Nm was determined.
- The linearity of the signal was confirmed by linear regression from 0.23 to 25 Nm. The coefficient of determination was $R^2 = 0.994$.

Therefore, on the validation of the experimental setup it should be possible to quantify the specific energy uptake during extrusion. A suitable in-process-control for twin screw extrusion was developed.

Effect of binder type and concentration on compactability of Acetaminophen granules

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Granulation is one of the most important unit operations in the pharmaceutical industry and is impacted by the materials used, the process and equipment; one important consideration is selecting the optimum binder. The binder influences particle size uniformity, tablet strength, ease of compaction and plays a major role in determining the physical properties of the tablet, which in turn can have significant effects on bioavailability and therapeutic efficacy.

In the present study, Povidone (Plasdone) wet granulation binders are compared to other common binders, hydroxypropylcellulose (HPC) and hydroxypropyl methylcellulose (HPMC) and at four use levels (1, 2, 3 and 5%) with Acetaminophen as a model drug. Granules were prepared using high-shear granulation equipment from two manufacturers (Formate -Pro-C-Ept and Niro).With the Niro granulator, binders were dissolved in water at use level of 1-5% and added to the drug as a solution, while with the Pro-C-Ept granulator; binders were added dry to the drug at the same use levels followed by granulation with water. The ampere reading and the impeller torque and product temperature were monitored to determine the end point of granulation. The granules were then sieved through an 18# mesh screen and dried in an oven at 60 deg C to a final moisture content of 2-2.5% w/w. The granules were then mixed with magnesium sterate (0.6%) and silica (0.1%) using a cone blender and compressed on an automated rotary press (Cadmach) with 12.5 mm flat faced beveled edge tooling at three different compression forces (18-20 KN, 38-40 KN and 48-50 KN). Tablets with all the binders were also prepared with 1% Crospovidone

(Polyplasdone) disintegrant and compressed at 48-50KN and evaluated for disintegration time and dissolution as recommended by USP.

At 1% binder level only Povidone K-90 provided tablets with acceptable breaking force and friability at all compression forces. At 2, 3 and 5% levels, tablets with Povidone K-25, K-29/32 and K-90 had higher strength compared to tablets with HPMC and HPC at equivalent compression forces. All tablets had acceptable friability of less than 1%. Further, the study also showed that method of binder addition did not have any significant effect.

Disintegration time ranged from ~ 1 min (HPMC) to ~ 8.5 minutes (Povidone K-90). All tablets met the USP recommended dissolution of 80% drug release in 30 minutes, except for tablets containing 5% of Povidone K-90 due to higher tablet strength.

Povidone was found to be a better binder as it provides better binding capacity at low concentrations producing hard, non-friable tablets. Although it provides tablets with high tablet strength, it does not significantly impact dissolution.

Evaluation of process analytical technologies for on-line particle size measurement

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The use of Focussed Beam Reflectance Measurement (FBRM) and Insitec (laser diffraction) technologies for the measurement of on-line particle size distributions (PSDs) of placebo granules was investigated, with a view to monitoring the milling process of dry granules.

The capabilities and limitations of these techniques were assessed with regards to sample particle size and mass throughput. The beam focal length, probe orientation and electronics filter setting were also investigated for the FBRM instrument. The effect of dispersion on the particle size distribution generated was also examined for the Insitec. The PSDs of three granule batches with volume weighted mean diameter ranging from 93 to 324 µm were measured both on- and off-line.

At the mass throughputs and sample batch volumes used in this study, FBRM was less suited to the measurement of on-line PSDs. The data generated were poorly reproducible, with the instrument incorrectly quantifying the size of coarse and fine granules samples. Particle agglomeration and the sticking of fine material to the probe window were identified as being disadvantages for this technique.

The Insitec instrument showed potential use for the on-line measurement of granule PSDs. The data were reproducible over a wide range of particle sizes indicating potential for process fingerprinting. Dispersion was necessary for accurate measurement of fine granule PSDs (agglomeration of granules causes the instrument to overestimate particles size). Data from the Insitec showed good correlation with those from off-line laser diffraction analysis for coarse granules without the need for additional dispersion of the sample.

The data measured in this study suggest that the Insitec was a better technique than FBRM for measuring the PSDs of dry granules, thereby offering potential for the measurement of granule PSDs in real time as they are being milled.

Fluid dynamics simulation of the high shear mixing process

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In this study, the Eulerian-Eulerian approach to model multiphase flows has been used to simulate the flow in a high-shear mixer. The advantage of using the Eulerian-Eulerian approach compared to Discrete Element Methods is that there is no computational limitation on the number of particles being modelled and thus, manufacturing scale granulators may be modelled as well. The simulation results are compared with experimental velocity profiles for the solids phase at the wall in the mixer obtained using a high speed camera.

The governing equations for modelling the dense mixer flow have been closed by using closure relations from the Kinetic Theory of Granular Flow (KTGF) combined with frictional stress models. The free slip and partial slip boundary conditions for the solid phase velocity at the vessel wall have been utilized.

The results show that the bed height could be well predicted by implementing the partial slip model, whereas the free slip model could not capture the experimentally found bed height satisfactorily. In the simulation, the swirling motion of the rotating torus formed was over-predicted and the tangential wall velocity was under-predicted, probably due to the fact that the frictional stress model needs to be further developed, e.g. to tackle cohesive particles in dense flow.

Foam-granulation technology (FGT): scalability in high shear granulation equipment

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The scale-up of conventional wet-granulation processes in the pharmaceutical industry involves powders of various sizes and properties. The issues surrounding these activities include selection and placement of spray nozzles, rate of liquid addition, and binder-liquid viscosity. The resolution of these issues is important to insure uniform distribution of the binder-liquid system. A novel technology has been developed that uses aqueous foams of conventional wet granulation binders. The advantages of FGT include the elimination of nozzles, the rate of liquid addition does not alter granule particle size distribution, typically requires lower liquid requirements during agglomeration, and enables uniform distribution of the binder-liquid phase throughout moving powder beds.

This paper is an initial evaluation of the scalability of foam-granulation technology conducted in high-shear granulation equipment at the laboratory (10 L), pilot (150 L), and manufacturing (600 L) scales. Immediate-release (IR) and controlled-release (CR) model tablet formulations were used in the study. In addition, a comparison was made between continuous and batch addition of foam for the CR model formulation at the manufacturing scale. Granulation and processing variables were scaled linearly from laboratory to manufacturing scale. Testing conducted on each trial included physical testing of the prepared granules and finished tablets as well as drug release (dissolution).

Results show that in the IR scale-up study, bulk and tap density measurements as well as tablet crushing strength values of the IR granulations were very similar from laboratory to pilot to manufacturing scale. The CR scale-up study also showed similarity in density measurements between scales. Crushing strength results reflected good tablet quality for all three scales, with the pilot scale trials showing the highest values. Particle size distribution tests based on sieve analysis showed good correlation between the three process scales for both the IR and CR formulations. IR drug dissolution tests showed a minimum of 80% drug released within 30 minutes for all tablets. CR dissolution curves were similar for tablets from all three scales. Overall, FGT appears to be a promising scalable granulation process.

Effect of granulation techniques on drug delivery

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The cost of synthesis of new polymeric materials and their safety has resulted in a new focus directed towards investigation of the use of polymer blends of pharmaceutically approved polymeric materials as matrix functional excipients to enhance single polymer performance. This also poses enormous granulation challenges to formulation scientists. This study aims at evaluating the effect of type of granulation on the release performance of a natural polymer obtained from fresh pods of *Abelmoschus esculentus,* a semi synthetic polymer, sodium alginate (NAG), and a synthetic polymer, carbopol 71.

Abelmoschus esculentus (Ae) gums were extracted from the fresh pods of *Abelmoschus esculentus*. Physical, thermal, sorption and functional properties of this derived natural polymer was elucidated. Scanning electron microscopy (SEM), particle size analysis, X-ray powder diffraction (XPRD), thermo-gravimetric analysis (TGA), differential scanning calorimetry (DSC), Fourier transform infra red (FTIR) and Nuclear magnetic resonance (NMR) were used to characterize the gum samples. The polymers were used as matrix agents at varying concentrations of 10 – 40 % w/w. Dry, wet, and droppill granulation techniques were used for drug formulation.

The DSC studies show that *Ae* had glass transition temperatures of 70 ^oC. Ae had no melting peak. Thermo-gravimetric analysis showed that weight loss was 14.98 % for *Ae* at 195 ^oC. X-ray diffractogram showed numerous broad halos for *Ae*. Droppills showed uniform appearance with coefficient of weight variation and percentage drug content between 0.1 to 0.5 % and 99.2 to 100 % respectively. Generally, granules had good flow and were non friable. Tablets of all the drugs showed acceptable mechanical properties. Formulation containing Carbopol 71 showed an inverse relationship between drug release and polymer concentration. The release of dk was influenced by the type of granulation and dosage form. Albendazole release from the tablet matrices in SGF and SIF was between 0.78-1.31 and 5 – 10 % respectively. Release in the rat ceacal content medium (RCCM) was between 70 – 85 % and lasted for more than 15 hours. Release kinetics using four models; zero order, first order, Higuchi diffusion model and Korsmeyer model, indicate the existence of more than one mechanism. The value of diffusion exponent 'n' changed with the change in polymer and pH of the dissolution media.

The results obtained in this study established the fundamental characteristics of the gum extracted from *Ae* and demonstrated the effect of granulation technique on drug delivery systems irrespective of the type of polymer.

Granulation of coke breeze fine for using in sintering process

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The coke breeze is the main fuel used in the sinter plants of Egyptian Iron and Steel Co. The most suitable particle size for coke breeze in sintering process is -3+1 mm. About 20% of total coke converted to fines (-0.5 mm) during different steps of manufacture. Introducing these fines during sintering process proves to be very harmful from different operation parameters. On the other hand, conversion of these fines into granules having suitable physico-mechanical properties will extend its application in iron ore sintering process. This study aims to investigate the production of granules from these fines by using molasses as organic binder and its application in sintering of iron ore. The results show that granules possesses highest mechanical properties were obtained with 14.5 wt % molasses addition. The sintering experiments were performed by using coke breeze in different shape (coke breeze after sieving -3+1 mm, coke breeze without sieving and coke breeze granules -3+1 mm). The reduction experiments, microscopic structure and X-ray analysis for the produced sinter were carried out to compare between their mechanical and chemical properties. The results revealed that, all sinter properties (such as compressive strength, productivity of sinter machine and blast furnace, reduction time and main chemical components) for produced sinter by using coke breeze with size -3+1 mm and coke breeze granules are almost consistent. The iron ore sinter which produced by using coke breeze without sieving has low productivity of both sinter machine and blast furnace. Also using of coke breeze without sieving in sintering of iron ore decrease the vertical velocity of sinter machine and increase the percentage of hematite in the produced sinter and consequently increase the time of reduction.

The enzymatic role in phthalate degradation by phthalic acid aerobic granule in sequencing batch reactor

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Phthalates, including phthalic acid (PA) and phthalic acid esters (PAEs), have wide application in industry and have become ubiquitous pollutants in the environment. However, the conventional activated sludge process cannot effectively treat recalcitrant phthalate wastewater. Bioaugmentation is one of the strategies for enhancement of the recalcitrant compounds degradation. A key ingredient for a successful bioaugmentation strategy is bioseeds selection.

The current paper reports experimental data involving phthalic acid-degrading aerobic granules (PA-degrading aerobic granules) used as bioseeds for enhancing PAEs degradation. Dimethyl phthalate (DMP) was selected as model of PAEs in this study. When degrading DMP, the system innoculated with PA-degrading aerobic granules can reach steady state in 15 days at an OLR of 3.0 kg COD m^{-3} d^{-1}. The highest OLR of 6.0 kg COD m^{-3} d^{-1} can be achieved by PA-degrading aerobic granules with a DMP removal efficiency of 100%. As comparison, the system innoculated with DMP acclimated activated sludge reached steady state in 54 days at an OLR of 3.0 kg COD m^{-3} d^{-1}. And the system can not sustain the OLR of 6.0 kg COD m^{-3} d^{-1}.

To probe deeper into the underlying reasons behind the successful application of PA-degrading aerobic granules as bioseeds, the variations of degradation rates and enzyme activities were traced in the DMP degradation process. The PA-degrading aerobic granules were found to originally possess constitutive enzymes catalyzing DMP and mono methyl phthalate (MMP) hydrolysis. They also have dioxygenase with high enzyme activity since they are cultivated with PA. During the DMP degradation process, the activity of esterase (DMP) increased from 1.01×10^{-3} to 0.112

U mg^{-1} protein. The activity of esterase (MMP) increased from 0.062 to 0.342 U mg^{-1} protein. A high activity of dioxygenase was maintained in the range from 0.097 to 0.133 U mg^{-1} protein. As a result, the reaction rates of DMP degradation changed from $k_1 > k_3 > k_2$ to be $k_3 > k_2 > k_1$, which makes the phthalate degradation proceed smoothly. Thus, it is quite important to keep the enzyme activity and the order of the reaction rates in $k_3 > k_2 > k_1$ in phthalates industrial wastewater treatment.

Caking of amorphous powders - material aspects, modelling and applications

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Caking of powders and bulk granules and adhesion of powders on equipment surfaces is a serious problem not only in the food industry. It can be demonstrated that amongst the different adhesion mechanisms responsible for such time consolidation the most relevant one is sintering of amorphous particles.

The tendency of caking is significantly elevated if there is a large amount of amorphous material present at the contact points between single particles. The viscosity of the amorphous materials decreases tremendously while exceeding the glass transition temperature (Tg). The higher the difference between glass transition temperature and storage temperature (T-Tg) the lower is the viscosity of the material (Williams, Landel, Ferry; 1955) and the faster sinter bridges between the particles are established. Since the glass transition temperature of water soluble amorphous materials is a function of the water activity the amount of water in the bulk heavily influences the caking process.

The building up and the growth kinetic of sinter bridges are also influenced by the force acting on the contact points between the particles. Therefore the deformation behaviour and the visco-elastic behaviour of the amorphous material plays an important role.

There are different methods available to quantify stickiness (which can be considered as the onset of time consolidation) and caking of powders. Fore instance caking can be quantified by time consolidation experiments performed in a ring shear tester. Based on the different models for the sinter kinetic (e.g. the one of Rumpf, Sommer and Steier (1976)) it is even possible to predict the level of caking. The obtained theoretical sinter bridge diameter can be correlated with the unconfined yield strength of the caked powder using a ring shear tester.

Wetting, disintegration and dissolution of agglomerated water soluble powders

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The reconstitution of agglomerated water soluble powders is usually considered to be composed of four sequential or concurrent processes:

1) the wetting of the powder linked to the pore size distribution, the contact angle and the liquid properties

2) the sinking of the agglomerates related to the balance between gravity and buoyancy forces

3) the disintegration of the agglomerates driven by the dissolution of the solid bridges created during the different processing steps

4) the dissolution of the initial particles depending on the physical state of the raw material.

This paper reviews the physico-chemical issues that food industry is facing when designing agglomerated product such as coffee, milk, instant infant formula or dehydrated soup and bouillons. The influence of various length-scales, namely the molecular-, the supramolecular- and the micro-structure of the product on the reconstitution process will be discussed. The molecular structure of most food matrix is complex and includes surfactants as well as hydrophobic and hydrophilic ingredients which complicate studying surface properties. Other effects on the molecular structure during the reconstitution process such as the swelling of certain carbohydrates or the denaturation of proteins will not be discussed. The supramolecular structure of food material varies from amorphous to the semi-crystalline to the crystalline state which changes dramatically the interaction of the product matrix with water. Finally, the microstructure depends closely on the process parameters during powder processing. Different methods including X-Ray tomography allow to assess particle and pore size distributions as well as porosity and diameter of solid bridges between particles in agglomerates. All these effects are decisive for the properties of the final food product, leading to an increased consumer acceptance.

Theory and numerical simulation of two-component granulation

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Most of the previous studies consider granulation of a single component (univariate PBE). Yet more often, granulation is a multi-component process. In addition to changes in the size distribution, one needs to know the compositional distribution of components among granules of different sizes. Ideally, all granules should have the same composition. In reality, actual composition varies with granule size and time. Theoretical aspects of the aggregative mixing have been recently studied in [1]. To extend the theoretical analysis from [1], a more general aggregation kernel is formulated in the form $K_{12} = k_{12}\,\psi_{12}$, where k_{12} depends on the size if the aggregating particles (granules) and ψ_{12} depends on their composition. For k_{12} we use the kinetic theory of a granular flow:

$$k_{12} = \hat{\beta}\psi_{12} d_{43}^{\gamma} .(d_1 + d_2)^2 \left(\frac{1}{d_1^3} + \frac{1}{d_2^3} \right)^{0.5}$$

where d_i is the diameter of particle i, which is assumed to be spherical. For ψ_{12}= 1 we have chosen the expression

$$\psi_{12} = \exp\left[-a_{AB}(c_1 + c_2 - 2c_1c_2)\right]$$

where a_{AB} is a parameter and c_i is the mass . By choosing the value of a_{AB} we can simulate a wide range of behaviors [1]. With a_{AB}=0 we recover the composition-independent kernel for which theory provides solutions.

The numerical challenges of this problem are quite significant [2]. In this study we apply three different techniques with complementary advantages and limitations and extend the analysis for kernels for which exact predictions are not possible:

(i) Direct solution of the discrete, two-component PBE. This rigorous and detailed approach is computationally demanding and can only be used to track the very early stages of granulation

(ii) Constant-Number Monte Carlo (cNMC). This method allows the computation of the bivariate distribution over arbitrarily long times. Its chief disadvantage is that is not well-suited for systems that involve space and time gradients.

(iii) Direct Quadrature Method of Moments (DQMOM): this methodology is very efficient in one-component systems and is currently the only viable option for interfacing the PBE with fluid dynamics. Extension to two-component systems is not straightforward and requires validation against known solutions.

We present results of simulations for various initial conditions in terms of amount of API and size ratio of the API and excipient particles. We find that Monte Carlo simulations provides very good agreement with the rigorous (discrete) PBE and also with the predictions of the theory. We present further results with both positive and negative values of the parameter a_{AB} and discuss the conditions under which the DQMOM method provides accurate solutions to the bi-component problem.

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New challenges for press agglomeration using roller compaction

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Fine dispersed bulk materials are processed with roller compactors to hard flakes and briquettes. Minerals, metals and chemicals have today much higher purities and are often more corrosive and abrasive than in the past. Extremely abrasive and corrosive products cannot be processed with usual materials of construction. Abrasion and corrosion have consequences to contamination of the products and wear costs of the equipment.

The target was to work without or at least with a minimum of contamination and to improve the service life of the equipment. The best options are metal free materials based on oxide ceramic mixtures, carbides and coatings. Unfortunately the mechanical and thermal shock resistance of this group of materials is rather poor compared to the high surface pressure requirements in a roller compactor. The durability of surface coatings caused further problems.

The current paper reports about interdisciplinary research work using finite elements and plasma physics. One main conclusion for the application of extremely hard and brittle ceramics was the use of a sandwich type design of the carrier materials. As a result a matrix was developed which allows a close consideration of the resistance against corrosion and wear versus mechanical and thermal requirements of the parts in contact with the product to be processed. This matrix compares conventional iron based materials with ceramic materials, fluorinated hydrocarbon coatings, plasma surface coatings, and physical and chemical vapour deposition and allows designing equipment, which is fully in compliance with the particular product properties.

Case studies of demanding applications (refractory and semiconductors) will be presented and an outlook will be given on future trends and requirements.

Scale-up and interchangeability of twin-screw granulators used for a continuous wet granulation process

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Scale-up for a continuous wet granulation process using a twin-screw granulator is obtained by prolonging the production time. However, sometimes there is a need for a larger production capacity to maintain a reasonable process time.

In this paper, scale-up of a granulation process was investigated using 2 granulators with different screw diameters (CONSIGMA™ 19 mm and 25 mm). To ensure that the granulation conditions were the same for both granulators, screw speed and material output rate were adjusted to obtain the same filling degree. Granulation experiments were run using 2 filling degrees: 16.5 and 22.0%. Furthermore, a comparison was made of different granulator types with the same screw diameter (APV Baker and CONSIGMA™ 19 mm). Based on the length-to-diameter ratio of the granulators the same screw configuration was used. The influence of scale-up and granulator type on oversized agglomerates (>3150 µm), yield (<1400 µm), median granule size, granule quality (friability and compressibility) and tablet properties (friability, tensile strength, disintegration time) was investigated using α-lactose monohydrate as a water-soluble excipient and dicalcium phosphate anhydrate as a water-insoluble excipient. Distilled water was used as granulation liquid; PVP was used as a binder.

The results show that scale-up had no effect on oversized agglomerates, yield, granule quality and tablet properties, regardless of the filling degree. For α-lactose granules, scale-up affected the median granule sizes at both filling degrees, indicating that the granulation process was dependent on the screw diameter and filling degree of the granulator. While changing the granulator type (CONSIGMA™ vs. APV Baker) had a limited effect on granule quality and tablet properties, the median granule size was

considerably influenced by the granulator type. For dicalcium phosphate granules, scale-up and granulator type did not influence oversized agglomerates, yield, median granule size, granule quality and tablet properties, independent of filling degree.

This study showed that scale-up could be done with only a limited effect on the particle size, while the interchangeability showed more challenging concerning particle size, granule quality and tablet properties.

Analysis of the product granulometry, temperature and mass flow of an industrial multichamber fluidized bed urea granulator operating at unsteady state conditions

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Within the wide variety of industries that utilize granulation to produce particles with defined properties, the fertilizer manufacture has an essential role in securing food supplies around the world. Urea in granular form is one of the most often used nitrogen-based fertilizers, being the global market conditions exceptionally favourable since 2007. In response to strong market fundamentals, the world urea capacity has been forecasted to expand from 136 Mt in 2008 to 192 Mt in 2011. In this context, knowledge improvements to operate more efficiently urea granulation plants will be extremely worthy.

The industrial fluidized-bed granulator for urea production often has several growth chambers which allow obtaining narrower particle size distributions, homogenizing the particles residence time. A growth chamber is basically a bed of solids fluidized by air where small urea particles are fed continuously and a urea concentrated liquid solution is sprayed from the bottom of the unit. The granules grow through deposition of the tiny liquid drops onto the seeds, followed by solidification of the urea present in the solution through cooling and evaporation of the droplets water content. The growing particles flow under-currently from one chamber to another. Usually cooling chambers, where no urea solution is supplied, are placed downstream the growth beds to meet specific requirements for further processing of the granules.

Currently, considerable trial and error is required to operate the industrial urea granulator. Its dynamics is complex and makes difficult to run the plant at steady state. Good operability of this key unit is essential to control several properties of the granules in order to avoid potential problems associated with the granulation circuit stability, urea storage, transportation and supply to the soil. Thus, the understanding of the fluidized-bed granulator dynamic behaviour is of great importance to produce granules with the desired attributes and achieve stable operations of the granulation circuit, preventing plant shut downs.

In this work, a complete dynamic model of a continuous industrial fluidized bed granulator for urea production is presented. Three growth and three cooling chambers in series are simulated. Non-steady state mass and energy balances are solved for all the fluidized beds together with the population balance equation (PBE). Since each granulator chamber can be modelled as a continuous stirred tank (CST), the multichamber granulator is represented by a series of CSTs. The PBE solution for non-steady state operations of continuous granulators with variable chamber solids mass has not been extensively studied. In fact, the granulators are usually modelled assuming constant bed mass to mimic the typical pressure drop control employed in industry.

By using the population, mass and energy balances, the open-loop behaviour of the granulator is analyzed. With this aim, and to further develop efficient control strategies, different step disturbances are assayed. Based on the results of the performed sensitivity study, some guidelines are proposed in order to select manipulative variables to maintain the product quality (granulometry) and granulator stability (pressure drop, bed height and temperature) within the desired values.

Crospovidone: a new pelletisation aid in wet-extrusion/ spheronisation

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Today, microcrystalline cellulose (MCC) is the reference standard as pelletisation aid in extrusion/ spheronisation, showing on the one hand ideal pelletisation properties such as narrow particle size distribution, high sphericity and suitable mechanical properties but on the other hand also with some known disadvantages such as prolonged drug release profile of low soluble drugs and drug decomposition to name these as an example. This was the reason to search for substitutes. In this context, crospovidone has proved to offer substantial advantages as a pelletisation aid.

As many new NCEs demonstrate a low solubility, a pelletisation aid which also offers the ability to turn low soluble active ingredients into fast dissolving stable pellets was looked for. Crospovidone proved to fulfil these requirements. Using paracetamol, hydrochlorothiazide and spironolactone as model substances, pellets of up to 60% (w/w) API were produced. The most distinguished differences between pellets based on crospovidone and MCC concerned the disintegration and drug release behaviour. Contrary to MCC pellets, the pellets containing low soluble APIs and crospovidone resulted in a fast release. It was proved that the described binary systems not only worked with low pressure extrusion but also with similar results by using high pressure extrusion techniques. The stability of the different crospovidone pellets was evaluated after 6 months of storage at RT. They showed no variation in all tested parameters.

Crospovidone changed its behaviour under temperature load and changed its surface in such a way that the hydration was slower, hence impairing the ability for a fast release and increasing disintegration values. Thus, the drying temperature is a critical process variable.

The crospovidone based pellets were coated with a gastro resistant film film without any difficulty using a Wurster coating processing technique. The drug release profile showed a safe protection against the gastric acid and released the API in the intestinal medium as expected.

Crospovidone shows an excellent behaviour as a pelletisation aid and produced fast releasing pellets even with low soluble APIs.

Electrostatic atomisation in fluid bed granulation – a formulation screening study

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Fluid bed granulation is a widely used technique in pharmaceutical industry. A Multichamber Microscale Fluid bed powder Processor (MMFP) has been developed for rapid characterisation of pharmaceutical materials. Previous studies have shown that to successfully make granules with this small scale equipment, it is necessary to use electrostatic atomisation to produce the granulation liquid droplets instead of pressurised air. This miniaturised device gives good possibilities to fast formulation development, as the granulation process is fast and small quantity of material is needed.

The aim of the study was to mimic the formulation development phase in the drug development, where the amount of active pharmaceutical ingredient can usually be very low. To better understand the effect of different excipients in the end product, three mixture designs were constructed. A model drug, acetylsalicylic acid and a crystalline excipient, α-lactose monohydrate, were used in all three designs. The third component of the mixture design was varied, it was either microcrystalline cellulose, dicalcium phosphate anhydrate or starch. Polyvinylpyrrolidone was used as binder which was added as a dry powder just before the mixing phase of the fluid bed granulation process.

Each point of mixture designs was granulated in MMFP using electrostatic atomisation. The process conditions including the amount of granulation liquid were determined beforehand and maintained for all the batches. After the completion of each granulation, the granule size distribution, friability and compressibility were measured for every batch and these were used as responses in multivariate modelling. The granule size distributions before and after friability testing were determined using a spatial filtering technique and a static surface imaging technology. Also, to determine the compression properties of the formulations, the granules were compressed to tablets using an instrumented eccentric tabletting machine.

This study demonstrated that it is possible to granulate different pharmaceutical materials in the MMFP using electrostatic atomisation. Differences in formulations were found which were linked to excipient functionality. There is still a challenge to find suitable and fast methods of analysis for small scale formulations, but image and laser based techniques used in this study provide promising options for future small scale characterisation.

Formulation design for optimal high-shear wet granulation using on-line torque measurements

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Formulation is typically the result of a combination of tradition and intuition, despite its relevance for both the final drug properties and the process control. Granulation, a critical operation in the pharmaceutical industry, is mostly affected by formulation; perhaps it is the process step where formulation mostly exploit its role of achieving a product with designed final properties.

In this contribution we present several quantitative measurements and speculations to achieve a predictive formulation design, from fundamental chemical and physical properties of the mixture constituents, in addition to on-line process measurements.

High Shear Wet Granulation (HSWG) has been addressed, because of its relevance in pharmaceutical industry and the availability of quite a large body of semiempirical knowledge in optimal formulation, to compare with. Monitoring the process using impeller torque, we aim at determining the onset of granulation and the optimal end point as a function of changes in formulation/in process parameters. Further, particle size distribution (PSD) evolutions is evaluated and correlated to different formulations and process evolution as reported by torque measurements. Experiments were performed in a vertical, top driven high shear granulator, using variations of a common, active-free formulation including MCC (Avicel PH101) and Lactose Monohydrate (150M and 200M) or Anhydrous as diluents, croscarmellose sodium as disintegrant and HPMC (Pharmacoat 603/Methocel E5) or PVP as binders, in addition to water.

The results indicated that the onset of granulation can be clearly and uniquely identified as a sudden increase in torque. By a suitable algorithm applied to the measured signal after filtration, a quantitative and reproducible identification of the onset was achieved and correlated to the added liquid volume. Once minimum liquid volume necessary for granulation (MLV) is identified, it has been correlated to PSD, water absorption capacity and solubility of the excipients as well as dry binder amount. Results have been processed to yield a "granulation map" useful for both formulation design and process optimization.

Gibbsite particles interactions and agglomeration during crystallization from Bayer liquors

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To date, most of the world's alumina (Al_2O_3) is commercially produced by the Bayer process. An important step of the process involves the crystallization of gibbsite (□-$Al(OH)_3$) from seeded, supersaturated caustic aluminate solutions at temperatures 60 - 90 ^oC. Gibbsite crystal growth is inherently slow; hence agglomeration is promoted for the production of coarse particles of commercial interest.

This work focuses on studies performed to elucidate the reluctance of colloidal size gibbsite crystals to undergo rapid aggregation and agglomeration during crystallization. Seeded, isothermal batch crystallization of gibbsite from synthetic liquors were carried out in which the role of alkali metal ion (Na^+ versus K^+) and the incidental particle interactions were probed at 65 ^oC. Interactions between gibbsite particles dispersed in supersaturated sodium and potassium aluminate liquors were quantified in terms of temporal interparticle forces (by Colloid probe AFM) and dispersion rheology.

The results show that both particle aggregation and agglomeration processes were faster in sodium than potassium aluminate liquors. Furthermore, strong repulsive forces which are not due to electrical double layer interactions, initially exist between gibbsite surfaces, delaying the on-set of aggregation and agglomeration. With time, the interparticle repulsion attenuated and completely disappeared, followed by development of adhesive particle interactions. The particle interaction forces and the rates of dispersion thixotropic structure, shear yield stress and visco-elastic moduli development were faster in sodium than in potassium liquors, consistent with the agglomeration rates. The findings underscore the important role the non- crystallizing alkali metal ((Na^+ versus K^+) ion plays in the interfacial phenomena underpinning the Bayer process gibbsite agglomeration mechanism.

Numerical determination of the stress distribution during die compaction processes

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Die compaction represents one of the most important manufacturing processes for pressure agglomeration of particulate solids. To obtain a desired product quality, besides the selection of the optimal machine parameters like compaction pressure, punch velocities and pressure dwell time the knowledge of material properties is essential. As the tabletting process mainly affects physical and mechanical properties of the product, knowledge of compaction properties for the used powder formulations is necessary to avoid manufacturing defects like capping or caking. One main reason for these defects consists of inhomogeneous stress distributions within a tablet. Although die compaction is a well established process in industry, direct in situ measurements of stress states occurring inside of a tablet during compaction are still not possible.

This paper describes the determination of the internal stress distribution during tabletting by numerical methods. By applying the Finite Element Method (FEM) the powder body is modelled as an elastic–plastic continuum. The Drucker–Prager Cap (DPC) model was chosen to describe the changes in material properties during die compaction. The model includes the yield surface of the material, which represents both failure and yield behaviour at different stress states. To calibrate the DPC model shear tests, diametrical as well as uniaxial compression tests were carried out to determine the shear failure behaviour of the considered powder. An instrumented compaction simulator has been used to determine the yield locus during the compression. In addition to the common instrumentation a specially instrumented die has been used to characterise the compaction properties for a wide range of different relative densities. The die sensor has also been used to determine the pressure dependence of the friction coefficient μ between powder and die wall.

Finite Element Analyses (FEA) have been carried out using the calibrated material model. The relationship between relative density of the powder bed and applied pressure is obtained from FEA and compared with the experimental data. The results show good agreement, which demonstrates that FEA can capture the main features of the powder behaviour during compaction by implementing the DPC model as appropriate material model. With FEA in combination with simple compaction tests determining the material properties it is possible to predict the compaction behaviour of new powder formulations. As a result, cost and time intensive experiments for the proper setup of compaction parameters can be reduced significantly.

Rheological measurement methods to predict material properties of fat based coating materials

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A huge variety of particles used in the food industry are coated with a protective layer for example to avoid reactions between particles in a mixture, to act as a spacer between particles or to avoid agglomeration and compaction. Besides a temperature controlled release of particles can be realised. On the one hand the coating layer has to be strong enough to go through the handling processes during the production process like mixing or conveying processes without any damages of the coating layer. Therefore the stability of the coating layer is an important parameter. On the other hand in some cases the coating layer has to be removed to get controlled release.

Common material tests in order to measure the breaking strength of substances do not provide sufficient results to characterise the mechanical stability of coating materials. Materials that have obviously differences in their hardness could not be divided by measuring the breaking strength in a texture analyser. Other materials do not break during the test, they just deform irreversible. In order to this, the results are not comparable.

The investigated fat based coating materials are viscoelastic solids. For the interpretation of rheological measurements a model that combines the viscous and the elastic part has to be used. In this study the Kelvin-Voigt model was used for the rheological interpretation.

Materials who had no differences in the braking strength measured by the texture analyser can be divided by the end of their viscoelastic range. The linear viscoelastic range of the investigated coating substances provides more detailed information of the material. The End of the viscoelastic range is characterised by the break of the material or by an irreversible deformation in the structure. Also the creep test performed with the texture analyser shows no significant increases in strain and no sufficient differences between the materials. However the creep test results of the rheometer identifies differences in coating materials and it has a better reproducibility, thus significant increases in strain can be detected.

Quantitative analysis of structure and transport processes in anaerobic methanogenic granules using Magnetic Resonance Imaging

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Reactors such as the up-flow anaerobic sludge bed reactor (UASB) employing anaerobic granular sludge are presently the most frequently used technology for anaerobic wastewater treatment. The activity of the granular sludge is often limited due to a restricted mass transfer of macronutrients, micronutrients and microbial products in the biofilm. Therefore, the mass transfer in the granule is of a high importance and must be studied intensively.

Magnetic resonance imaging (MRI) is a non-destructive, non-invasive method that can be applied under *in situ* conditions. MRI presents a good method to study metal transport in porous matrixes such as catalyst bodies, sandy soils or biofilms. It can also be used to reveal the inner structure of the granules and to describe the transport properties (diffusivity) of the water contained in the granular matrix.

This presentation will show quantitative metal transport measurements in the anaerobic granular sludge using spin-lattice relaxation time (T_1) weighted MRI. Single methanogenic granules were exposed to 1.75 mM FeEDTA solutions and the consequent penetration of iron into the granule was followed in time. Using the 3D Turbo Spin Echo (TSE) imaging method, a spatial resolution of $109 \times 109 \times 218\ \mu m^3$ and a temporal resolution of 11 min was achieved. A method to recalculate the obtained intensity data to real iron concentrations was developed. The data obtained allowed evaluation of the diffusional properties of the granular matrix. The calculations were performed in three dimensions, revealing that the diffusion within the granule is rather homogeneous, without strong deviations caused by the granular matrix.

The inner structure of the granules was described. Regions with extremely low water content and low diffusivity were indicated in some types of methanogenic granules, whereas other types of granules were shown to be rather homogeneous and highly diffusive. These differences where mainly related to the different content of the precipitates in the granules. Whereas granules grown on complex substrate (paper-mill wastewater) in the presence of various metals (calcium, iron, etc.) were highly heterogeneous, granules grown in methanolic wastewater were homogeneous.

The present results will allow calibration of models describing mass transfer within methanogenic granules. Whereas the concentration profiles of e.g. oxygen, nitrate or sulfide have commonly been measured by microelectrodes, selective microsensors for heavy metals concentration measurement are not yet available for measurements in biofilm. Therefore, the present study brings information on metal transport within methanogenic granule that to date can not be obtained in another way.

Reactive binders in detergent granulation: understanding the relationship between binder phase changes and granule growth under different conditions of relative humidity

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The increasing tendency to enhance consumer products with added functionality is leading to ever more complex products that are manufactured at large scale in conventional processes. Hence, it is important that process operating conditions are matched to the product requirements. We report on the fundamental characteristics of the reactive binder, LAS acid (HLAS), used in detergent granulation, in relation to its wetting behaviour and viscosity as it is neutralised by its reaction with sodium carbonate, and how the phase changes are affected by relative humidity (RH) and temperature, in order to establish the relationship between the binder phase changes and granule formation and growth. We have found that the higher the degree of neutralisation, the lower the tendency of the liquid to wet the particles (the binder behaves as a sticky paste) and that wetting behaviour is strongly dependent on RH. The latter highlights the importance of controlling the environmental conditions during processing and storage of the materials.

Recrystallization of naphthalene from toluene using antisolvent CO_2

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Supercritical fluid processes are promising methods of granulating fine particles by which fine particles can be granulated without using carrier particles or using any binder which may remain as an impurity. Due to production of granulated fine particles, reliable measurement and prediction of phase behaviour of the ternary and quaternary systems are essential. In this work, the phase behaviour of the ternary system of Naphthalene+Toluene+CO2 has been studied experimentally. In each experiment, a solution of Naphthalene in Toluene was expanded using carbon dioxide as the anti-solvent. A pressure-volume-temperature (PVT) apparatus was used for measuring bubble point curves, and the solid–liquid boundaries. Results are reported for this ternary system at carbon dioxide concentration ranging from 54.3 to 86 mol%, and within temperature and pressure ranges of 288–313 K and 3.81–7.59 MPa, respectively. It has been observed that at lower initial concentration of Naphthalene in Toluene, CO_2 acts as co-solvent and it is difficult to precipitate dissolved solute. On the other hand by increasing initial concentration of Naphthalene, CO_2 significantly affects the optimum operational conditions of the GAS process and it is possible to precipitate most of the dissolved Naphthalene as fine particles within temperature of 288-293 K. the precipitated particles has been analyzed by SEM system. The SEM micrograph showed that the Naphthalene can be micronized properly. The Peng-Robinson equation of state (PR EOS) has been used in correlating the experimental data. The results showed that the PR EOS can accurately correlate the experimental data for the bubble pressure of the ternary system.

Textural analysis of acrylic polymer-based pellets using SEM images

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The surface texture and the inner structure of the pellets strongly depend on drug proportion, composition and volume of the wetting liquid, additives and spheronization and drying conditions, and critically determine relevant properties such as friability, flowability, wettability, adhesion to various substrates, and drug delivery behavior. Image analysis of scanning electron microscopy (SEM) micrographs can provide quantitative information of fractal geometry and surface texture of pellets, using the intensity, position and/or orientation of the pixels.

The present work focuses on the application of the textural analysis of gray level SEM images for obtaining the gray level non-uniformity (GLN), the fractal dimension of pellet surface and other parameters derived from the gray level co-occurrence matrix (GLCM). Several cellulose pellets formulations differing in the proportion of acrylic polymers were prepared under various experimental conditions and then the roughness and the pore size distribution at pellet surface were characterized using image analysis. Drug release profiles were obtained and the correlations between release rate and the parameters derived from the image analysis were explored.

Image analysis of SEM micrographs enables a precise characterization of the morphological features of pellet surface and in their dependence of pellet composition. Furthermore, the parameters derived from the image analysis have a great predictive value regarding both the rate and mechanism of drug release from pellets.

Process control; where understanding, modelling, and online monitoring come together

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Binder granulation is a multivariate process involving multiple transformations[1] in a single unit operation. In addition, overall granulation systems have ancillary equipment[2] that contribute to the control problem, and often have recycle loops that further complicate the control challenge. As such, granulation process control requires a level of multivariate understanding that is at best challenging and at worst untenable for a true "centreline" operation. On many production sites around the world this understanding is in the experience of the operators and hidden in rigid and sometimes fragile operating procedures. This paper aims to present how the knowledge that has been gained in the last decade by the granulation community can play a role in improving the control of our processes. By using structured methods for process control, we identify key areas on where to focus future research efforts.

This paper presents a case study of an academic-industrial collaboration, the "Control of Binder-Powder Agglomeration" project sponsored by the International Fine Particle Research Institute (IFPRI) with the Doyle Group at UCSB. We include a survey of the work done to date, including complementary academic research and industrial pilot studies. The academic efforts include simulations employing Model Predictive Control with many interacting process variables, various Population Balance Models, and model reduction for control applications. Pilot studies include methods development for in-line sensing of agglomerate size combined with other attribute and process data to derive empirical control models via standard system identification and PCA and PLS methods.

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[1] Typical transformations include binder dispersion, nucleation, growth, consolidation, breakage, etc.
[2] Typical ancillaries with control interactions include powder feeders, pumps, dryers, classifiers, etc.

Dry water: from physico-chemical aspects to process related parameters

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Water rich powders known as "dry water" consist of aqueous liquid droplets encapsulated by a protective shell formed by self-assembled superhydrophobic nanoparticles. The water-rich product contains considerable amounts of aqueous liquids (up to 98 %w/w). However, despite this large amount of liquid, the product possesses the same flow properties as a dry powder. Water can be easily released by mechanical stress, e.g. by rubbing it onto the skin. The process does not make use of any organic solvent and can be easily developed in industrial scale. The process can also be used for vectorisation of water-soluble active agents.
Although "dry water" is known from 1960s, it is only recently that fundamental mechanisms of water encapsulation in dry water were described.

This paper aimed to present the state of knowledge on dry water formation, from physico-chemical considerations to process related parameters. Some of promising aspects, potential applications as well as future orientations are also presented.

Investigations of the correlations between granule microstructure and deformation behaviour

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The bad flowability of powdered materials is one of the reasons, that make an agglomeration step essential to improve the handling properties e.g. for die pressing. With the help of agglomeration processes like fluidized bed granulation or spray drying it is possible to generate ceramic material mixtures with specific tailored properties from water or solvent based suspensions. By varying the properties like granule density, size, shape, internal or external structure it is feasible to conform the produced bulk to following processing steps.
The agglomerates need to have a good flowability (round shape, low fines content) e.g. for die filling processes as well as a defined strength to withstand handling processes as transport, dosage or storage. Contrary to this it is essential to obtain a complete destruction of the granules during die pressing to achieve homogeneous green and sintered prototypes without defects. Granules have to be disintegrated into the primary particles through the compaction process.

During several experiments it became apparent, that besides the polymeric additives the internal structure of the spray dried agglomerates is one parameter, which affects the deformation behaviour of the granules and with this the microstructure of the produced compacts. It is possible, to measure the single granulate deformation and fraction behaviour in the Fraunhofer Institute in Dresden with the help of special equipment for sizes > 40 µm. For correlation of size, deformation and structure, spray dried alumina in the size class 63 – 100 µm was characterised by measurement of deformability and internal structure.

Several methods were investigated to characterise the internal structure of granules, which can be described as the spatial distribution of primary particles and eventually added organics in a defined space. All techniques use the porosity as parameter for characterisation. The porosity of a loose bulk of granules was estimated with the help of mercury intrusion porosimetry. The results were compared to the porosities, measured with image analysis software on SEM images of polished surfaces of the internal structure of single granules. Additional it was tried to calculate the porosity from mass and volume of single granules and to get information about the porosity by using computer tomography. The results were compared to select the best method to characterise the internal structure via porosity.

Especially the SEM images of polished granule surfaces (broad ion beam preparation) and the computer tomography images showed the scattering of real internal granule structures: hollow and homogeneous granules (fig.1 and 2), characterised by the factor H, defined as quotient of the average diameter of the internal void and the average diameter of the granule. The samples were spray dried from suspensions with almost the same solid content in the suspensions and slightly modified amounts of organics.

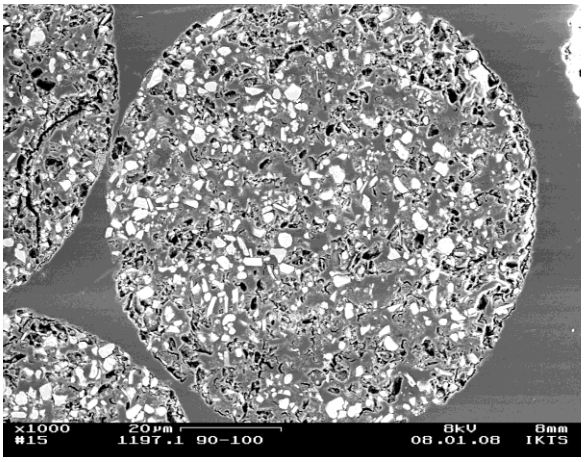

Figure 1: Homogeneous Al_2O_3 granule

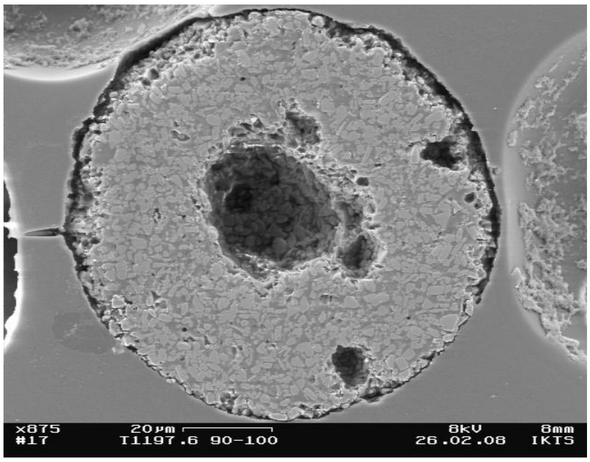

Figure 2: Hollow Al_2O_3 granule

These granules with an extrema internal structure were forced to undergo deformation analysis using the single granule strength tester. From the deformation curves, correlations to the internal structure were obvious: hollow granules seem to deform with a strong increase of force until the breaking point is achieved. Then, the force drops to a lower, in some cases even to the zero level. After this the force increases again with further destruction of the fractured granule. Homogeneous granules do not show such an intensive breaking point, the force and with it deformation increases more constantly.

Some aspects of granulation of colloidal disperse ceramic material mixtures

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Products based on ceramic raw materials have a key position in different industries. Under high temperatures and abrasive and corrosive conditions enable high strength and hardness, low weight and adjustable functionality of the material new technologies with high reliability.

The properties level can be increased by processing of sub-micron raw material with high purity as produced by gas phase synthesis. To tailor the properties, mixtures of the basic component with small amounts of ceramic or metal additives have to be prepared. This requires a mixing technology with high energy input to provide deagglomeration and mixing and the transfer of homogeneity into the granulated state. The selection of the granulation technology is determined by the following processing steps of the resulting bulk material: transport, disintegration, dissolution, compaction, thermal spray deposition. Thus homogeneous mixtures of primary particles, bulk material with defined functionality or beads with dense or porous structures are in the focus of product design of disperse ceramic raw material. The related granulation technologies are: compaction, pelletising, intensive mixing, fluidized bed processes, spray freeze granulation, spray drying.

The basic technological route in the ceramic industry is the processing of the raw material by wet comminution and spray drying to ready-to-press bulk material. The properties of the resulting bulk are determined by powder and suspension properties, addition of polymeric components (dispersant, binder, lubricant) and spray drying parameters. A complex granule and bulk characterisation describes:

> Granule size distribution, granule structure and density, granule shape, granule strength and deformation as well as the processing properties flowability and compaction behaviour.

The possibilities of tailoring the granule and bulk properties are demonstrated with an alumina material system. The influence of solids content, polymer composition, drying temperatures on granule structure (external shape – internal solids packing), mechanical granule properties and compaction behaviour and on sorption properties are described.

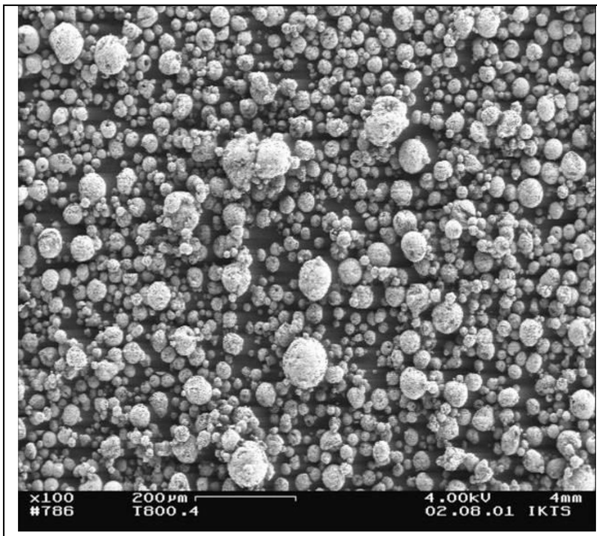

Fig. 1 Press bulk (Si_3N_4), prepared by spray drying

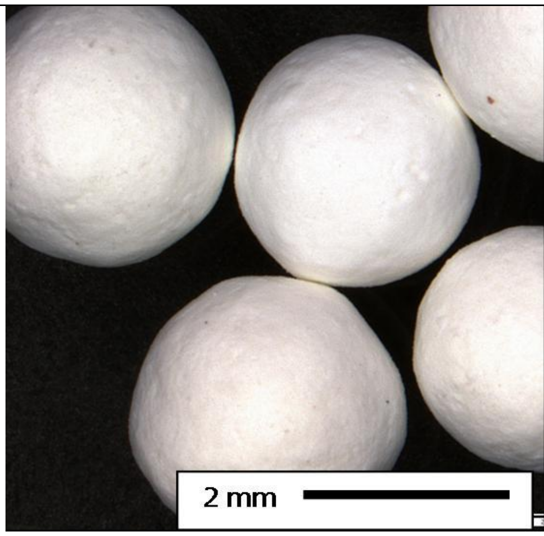

Fig. 2 Catalyst (ZnO), prepared by fluidized bed granulation

The comparison of properties levels realized by spray drying and spray freeze granulation demonstrate the potential but the problems of spray freeze granulation technology too.

The fluidized bed processes offers broad possibilities of preparation of bulk with large, monodisperse size distribution. The granules can be tailored to homogeneous, dense, defectless beads (milling material) in the range 200 µm – 2 mm or to catalyst bead material (hollow – homogeneous – graded) with improved functionality as explained by different examples.

Some development rules for proper product design, especially for press bulk development, are given as summary.

An experimental study of agglomeration in spray driers

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Agglomeration in spray driers occurs by overlapping the spray patterns of multiple liquid nozzles and the airstreams containing recycled fine powder. In this work, the role of the recycled fines stream is explored by measuring the extent of agglomeration between a single spray stream and a powder curtain. Two scales are investigated, a small scale drier with nominal capacity of 0.5-7 kg/h and a pilot scale drier with nominal capacity ~80 kg/h. Experiments were designed to investigate a number of parameters at three levels: low, medium and high about midpoints that represent typical operation at each scale. These operating points are representative of those available, or potentially available, to operators of agglomerating spray driers: spray flow rate, spray solids concentration, spray droplet size, powder flow rate, spatial number density of powder, and powder particle size. Drying conditions were kept as constant as possible and all experiments used skim milk powder. A measure of success, called the extent of agglomeration, was developed based on the proportion of particles sizes that disappear from the feed and then appear in the product. Comparisons were made between the reference case of natural agglomeration when the drier was run without fines, and later trials with fines. These show that fines addition does promote agglomeration. Comparisons between trials containing fines show that the extent of agglomeration depends principally on the mass flux ratio of fines to spray followed by the particle size of the fines; this can be linked to the probability of interaction between spray and fines in the turbulent interaction zone. The concentration of the spray liquid is a weaker effect which is only present when larger fine particles are used; it relates to the development of surface stickiness which influences the success of collisions. The two scales of drier have the same trends and approximately scale.

Application of low-substituted hydroxypropyl cellulose (L-HPC) to dry granulation

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Dry granulation is a process to make granules typically by using a roller compactor followed by low-shear milling. Since it doesn't require water or organic solvents, water-sensitive drugs can be granulated without interaction or environmental problems. Processing time can also be reduced since the drying process is not necessary. Low-substituted hydroxypropyl cellulose (L-HPC) is a pharmaceutical excipient which has been widely used as a disintegrant for tablets and granules. Since L-HPC has a good compressibility, it also works as a dry binder in tablets. Currently, the most common application of this excipient is to produce tablets through wet granulation or direct compression process. In the present study, performance of L-HPC in dry granulation was investigated. As a test formulation, powder mixture consisting of paracetamol (20 %), L-HPC or other binder / disintegrant (10 %), and lactose (70 %), was applied to a roller compactor (model TF-MINI, Freund Industry, Japan) to prepare flakes. Various grades of L-HPC having different particle sizes and particle shapes (fibrous or non-fibrous) were tested to compare performance. The flakes were further milled using a low-shear mill (model M-10, Yamato-Kakou, Japan) to adjust particle size. The obtained granules were evaluated by physical testing such as bulk density and flowability, and tablets were prepared from the granules using a rotary tableting machine (model Vergo, Kikusui, Japan). The tablets were evaluated by measuring hardness (Erweka, Germany) and disintegration time (JP). Results indicated that grades of L-HPC which have small particle size or greater plastic deformation showed higher binding strength with reasonable disintegration time. By choosing a proper grade, the formulation using L-HPC showed both a sufficient binding strength and disintegration time in dry granulation process without using additional binder or super-disintegrants.

Process analytical technology and multivariate analysis for process understanding, monitoring and control

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Process Analytical Technology is taking central stage in the new regulatory framework. The pharmaceutical industry is entering a new era. Quality by Design, Design Space, Process Signatures, are some of the terms that are now used frequently. Multivariate analysis has played an integral part for the real time development of process analytical measurements (multivariate calibration) and it is ready to face the challenge of Process Analytical Technology in this wider definition. In this presentation it is demonstrated that multivariate, data based statistical methods, play a critical role in deriving the Design Space, establishing a Control Strategy, establishing procedures for Continuous Verification and Real Time Release. It is shown that while some Real Time Analysers may be required for Real Time Release, there is a wealth of information in the process data that can be retrieved in the form of Soft Sensors, thereby providing a different (and frequently cheaper) alternative to analysers. Examples from applications to Granulation / Compression will be shown

Lab scale fluidized bed granulator instrumented with non-invasive process monitoring devices

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Fluidized bed granulation is a common size-enlargement process in pharmaceutical industry, in which a fine powder is agglomerated using liquid binder to get larger granules. However, fluidized bed granulation is a complex process in nature, and it is hard to control due to the strong interactions between different process variables, such as moisture content and granule size. Since the granule size distribution is one of the main characteristics of the evolution of the granulation process, there is a need to design process controlling methods to monitor the size distribution. In order to guide the process via correct pathway, one should be able to monitor the process i.e. measure the process variables inline.

In this study, the acoustic emission, flash topography particle size analyzer, multipoint-NIR and multipoint-Raman probes were instrumented into a lab scale fluidized bed granulator for simultaneous pharmaceutical granulation process monitoring. Parallel techniques were used in characterizing granule size distribution, mixing integrity, moisture content during fluidization. Granulations were carried out in a custom made modular top-spray granulation chamber.

The estimated granule size distribution and moisture content were compared to the values measured with offline reference methods. The molecular transformation process was monitored in order to see true end points for mixing, agglomeration and drying. Ability to perform measurements at different locations of the chamber gives information that single point measurements can not offer. This is crucial when the

measurements are the footsteps for the knowledge. These process monitoring methods are non-invasive and they are applicaple to other fields of industry, too.

Granulation, microstructure and dissolution of reactive microcapsules

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In situations where unstable and/or mutually incompatible formulation ingredients need to be incorporated into a granule, microencapsulation of the ingredients prior to their granulation is a possible way of obtaining a stable product. However, relatively little is known about the granulation characteristics of microcapsules and the subsequent release kinetics of the active ingredient(s) – in particular the relative importance of granule structure vs. microcapsule individual dissolution kinetics on the overall release rate.

We will present a comprehensive study of the relationship between microcapsule individual characteristics, granule structure, and the release kinetics of active ingredients for a case where the active is formed in-situ by a chemical reaction from precursors that have been previously encapsulated. Two methods for encapsulation have been used – spray drying for solid ingredients and complex coacervation for liquid phase ingredients. Solid microparticles were produced in each case, and these were subsequently granulated using a fluidised bed granulation process.

Depending on the properties of the individual microcapsules, the reaction kinetics between the ingredients, and the binder type (matrix vs. bridge forming), three qualitatively different regimes will be described: (i) granule dissolution-limited release; (ii) microcapsule dissolution-limited regime; and (iii) reaction-limited regime. Methods for optimising the hierarchical granule structure in order to obtain a required release profile will be discussed.

The microscopic study of granulation mechanisms and their affect on granule properties

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The granulation process is important in a wide range of industries, especially pharmaceutical, food and chemical. Within the pharmaceutical industry there are some special desired properties of granulated products like reduced inhalation and explosion risks, homogeneity of the components, and controlled dissolution rates. Fundamental understanding of sub-processes is required to control granulation behaviour and obtain a product with desired properties, this remains an important target for the researchers. Granulation mechanisms include: wetting and nucleation, consolidation and growth, and breakage and attrition. Each of these mechanisms become dominant at different granulation times, and have a strong impact on the evolution of the granules structure . They also lead to non-uniformity in the granule properties, even within the same size range. This work based on a microscopic level, single granule scale, and has been conducted to investigate the granulation mechanisms and the effect of these on the uniformity of the granule structure, binder content, porosity, dissolution rate and strength of granules within a given size class in high shear granulation. Based on the different structure of the granules at different massing times and the appearance of each structure, the results show how the granules coalesce, consolidate and break. It was found that significant in-homogeneity existed in the granule properties, even for granules of the same size and sampling time. It was found that 'coalescence granules' are more porous, weaker, have lower binder content and dissolve faster than granules having undergone a consolidation process. It is important that this inhomogeneity of granule properties should be considered in the formulation, endpoint determination and process control of high shear granulation. This also proves the importance of the individual rates of granule coalescence, consolidation and breakage on the granule properties, the understanding of which is crucial if theory is to be successfully incorporated into common industrial practice.

Effect of particle solubility and surface roughness on granulation kinetics in a bottom-spray fluidised bed process

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Pharmaceutical wet granulation generally involves the agglomeration of at least two types of primary solid particles (excipient and API) by means of a liquid binder in a mechanically agitated or fluidised bed process. Although the particle size of the two components can be matched if desired, the solubility in the binder and the particle morphology (surface roughness) of the two solid ingredients can often be very different. The objective of our work was to investigate the effect of primary particle solubility and surface roughness on the agglomeration rate of binary powder mixtures in a bottom-spray fluidised bed granulation process.

We will present the results of an experimental study involving the granulation of several pharmaceutical excipients with varying surface roughness (smooth – Avicel; medium – lactose and mannitol; rough – ATAB) and solubility in water (high – Avicel, lactose; medium – mannitol; low – ATAB) and demonstrate that their granulation kinetics proceed in two distinct stages: an induction period characterised by particle coating and limited agglomeration, followed by an agglomeration period with a more profound particle size growth. The duration of the induction period is strongly correlated with both surface roughness and solubility in the binder. We explain this behaviour on the basis of meso-scale mathematical model of wet agglomerate structure, showing that the accessible binder fraction and its viscosity can vary widely for the same binder/solids ratio depending on the primary particle surface roughness. We further show that the growth kinetics of binary powder blends can be predicted to a high accuracy from the knowledge of pure-component growth rates, using granulation kernels derived from meso-scale simulations.

Parametric sensitivity of granule microstructure on the distribution of local processing conditions in a low-shear granulator

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The properties of granules produced in most laboratory or industrial scale granulation processes are not uniform but follow a certain distribution. While the distribution of size can be “corrected” by milling the oversize and recycling the fines, the distribution of attributes related to the granule internal microstructure – e.g. composition or porosity – are difficult to fix once they deviate from specifications. The granule microstructure is the result of the local processing conditions (shear rate, particle collision frequency and velocity, etc.) that each granule experiences during its residence time in the granulation vessel. The distribution of granule properties is therefore related to the distribution of the local conditions within the vessel. In order to design a robust granulation process and to be able to predict the variation of granule microstructure during scale-up, the relationship between the distribution of local conditions and the distribution of the resulting granule microstructures has to be known. This involves two steps: *(i)* the characterisation of flow pattern in the granulator of interest; and *(ii)* the study of the influence of this distribution on the granule attribute of interest. In this work we will present the results of a computational study composed of the above two steps for the specific cases of fluidised bed and mechanically agitated granulators, whereby a combination of CFD simulation at the process scale and discrete particle modelling of granule microstructure formation at the particle length-scale will be used. We will show the relative sensitivity of granule microstructure to variations in both process- and formulation-related parameters, and present guidelines for preserving granule microstructure characteristics during scale-up.

Numerical investigation of effects of agglomerate property and flow condition on the powder dispersion in a simple inhaler

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In recent years there has been high commercial interest in the pharmaceutical industry and biotechnology to develop dry powder inhaler. Dispersion is defined here as the process of dispersing a powder as an aerosol containing fine particles (< 5 μm) suitable for inhalation into the lung. Previous studies of the inhaler dispersion efficiency have primarily been undertaken to compare commercial product performance from which a fundamental understanding of the dispersion process cannot be acquired.

This paper presents a numerical study of the dispersion process of pharmaceutical powders in a simple inhaler by means of combined CFD-DEM models. In this model, the motion of powders is obtained by DEM which applies Newton's laws of motion to every particle and the flow in the inhaler is described by the local averaged Navier-Stokes equation that can be solved by CFD. The swirling flow conditions, such as flow rate and turbulence intensity, and the properties of agglomerates, such as particle size distribution and cohesion, are varied to investigate their effects on the dispersion efficiency which can be estimated by the size distribution of fragments from the outtake. Based on the simulation results, the microscopic properties of fluid and powders are analysed and the dispersion mechanisms are investigated in terms of particle-particle, particle-fluid and particle-device interactions. Such understanding of dispersion mechanisms is critical to improving the efficiency of dry powder inhalers.

A new approach to the granulation of cyclodextrin inclusion complexes

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Cyclodextrins (CDs) are annular oligosaccharides containing 6 to 12 glucose unities joined together by alpha - 1,4 bonds. They have a conical-truncated shape with a lipophilic cavity in which different molecules can be included resulting in a stable inclusion complex. The cyclodextrins have been widely applied in pharmaceutical technology with the objective of increasing the solubility, stability and bioavailability of drugs in different pharmaceutical dosage forms, such as tablets.

In order to obtain β-CD tablets, liquid dispersions of drug/ β-CD are usually submitted to different drying processes, like *spray drying*, freeze-drying or slow evaporation, being this dry material added to a number of excipients. However, such drying processes can generate particulate materials showing problems of flow and compressibility, needing their conversion into granulates by means of wetting with granulation liquid followed by drying. In this work, the main objective was to evaluate the possibility of preparing tablets without the need of this extra drying step.

For this the acetaminophen / β-cyclodextrin liquid dispersion and the excipient were directly mixed. Acetaminophen was used as model drug due to its low water solubility and the inexpensive and widely available cornstarch was chosen as excipient. Acetaminophen powder was added into a β-cyclodextrin solution prepared in distilled water at 70ºC. Stirring was kept until this dispersion cooled to room temperature. Then cornstarch was added and the resulting dispersion was dried in spouted bed equipment. This material was compressed into tablets using an Erweka™ Korsh EKO tablet machine.

This innovative approach allowed the tablets preparation process to be carried out with fewer steps and represents a technological reliable strategy to produce β-cyclodextrin inclusion complexes tablets.