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| 190 | IDENTIFY SOLID AND GAS FLOW PATTERNS IN BUBBLING FLUIDIZED BED AND THEIR IMPACT ON SOLID MIXING BASED ON OPERATIONAL CONDITIONS | Yuning Li1,2, Kai Zhang2 & Xianfeng Fan1 | 1. Institute for Materials and Processes, School of Engineering, University of Edinburgh, UK  
2. North China Electric Power University, Beijing, China | Oral |


1. MICROSTRUCTURE OF MICRO-CRYSTALLINE CELLULOSE BASED GRANULES PRODUCED BY HIGH-SHEAR WET GRANULATION WITH LONG WET-MASSING TIME

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It has been demonstrated recently that steady states can be reached during agglomerate growth and break-up in high-shear wet granulation (HSWG).[1] Extended granulation time can be required to allow establishment of a steady state. In [1], a micro-crystalline cellulose (MCC)-lactose blend was used. This presentation is focused on characterization of the resulting microstructure of MCC-containing granules produced by HSWG with extended time. It is typically assumed, with HSWG, that agglomeration preserves the size and shape of insoluble particles like MCC. Instead, here, the microstructure evolves with extended mixing to a continuous MCC matrix with embedded lactose particles. Lactose particles can be removed by dissolution, leaving a highly porous MCC-based skeleton. The effect of wet massing time, liquid level, and MCC content and characteristics, on the formation of the microstructure is reported.

**2. PREDICTIVE FORMULATION DESIGN TO OPTIMISE HIGH DRUG LOADED ROLL COMPACTION FORMULATIONS**

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As the dose and therefore drug loading increases for a new pharmaceutical formulation, there is a general trend towards selection of wet granulation over roll compaction [1,2]. The drivers for this are typically related to challenges with flowability and low tensile strength due to loss in compactability coupled with poor active pharmaceutical ingredient (API) compaction properties.

Farber et al. [3] describe the "loss of compactibility" that is observed when a formulation is roller compacted and milled, before compression. The resultant tablets typically do not develop as much strength as tablets made by direct compression of the ungranulated blend. The unified compaction curve model [3] allows this loss in tablet tensile strength after roller compaction to be taken into account whilst still maintaining usage of the same tabletability (tensile strength vs. compaction pressure) relationship for a given material. This analysis can be further modified in order to provide a description of the material compactibility (tensile strength vs. porosity) as a function of ribbon porosity [4].

The loss in compactability of three common pharmaceutical excipient fillers has been characterised and described using a new loss in compactability model. Combined with a new methodology for prediction of powder mixture compactability, a standardised formulation capable of supporting a range of APIs at increased drug loadings was identified. These tablet formulations have been investigated using a full factorial DoE, designed to optimise roll force, roll separation and mill screen size with respect to granule flowability and compactability.


3. USE OF AN EXPERIMENTAL DESIGN FOR THE DEVELOPMENT OF A NIR IN-LINE FLUID BED GRANULATION MONITORING METHOD

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The aim of this study was to evaluate the Viavi microNIR™ spectrometer as a Process Analytical Technology (PAT) tool for monitoring and end-point determination of a fluid bed granulation process. Compared to classical NIR spectrometers, microNIR™ relies on linear variable filter technology and lacks any moving components, which in turn leads to an improved robustness to operating conditions.

A D-Optimal experimental design was set up, with spraying rate and inlet air temperature as independent inputs. The microNIR™ PAT wireless apparatus for on-line monitoring was positioned directly on the expansion vessel wall avoiding any interference with the process or formulation. During the granulation NIR diffuse reflectance spectra were acquired every 10 seconds in the 950 – 1650 nm domain with a resolution of 7 nm. Pre-processed spectral data and principal component analysis (PCA) were used to develop a multivariate model which allowed monitoring of different steps during the granulation process. The specific spectral values from the first overtone region were used for monitoring the water content. The best model fit with $R^2$ greater than 0.97 for three main components was calculated using the 2nd derivate values of the spectral data. This spectral pre-treatment can also be calculated using the Viavi microNIR™ OnSite software, facilitating the in-line process monitoring. In order to prove the detection capacity of the spectrometer for the granulation process monitoring, validation experiments were performed in optimal and extreme process parameters. The changes of the process parameters were well underlined during the process monitoring by the PCA analysis.

The results suggested that the in-line monitoring of granulation steps and moisture content facilitates the process control, leading to a product with optimum characteristics and greater reliability of the process itself. Also, the process analyser based on linear variable filter technology is sensitive enough to distinguish between different steps of the process.

![Score line plot for the most relevant experimental runs, projection of the first principal component observations.](image)
4. MULTI-STAGE GRANULATION: AN APPROACH TO ENHANCE FINAL GRANULAR ATTRIBUTES

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A new process step in granulation has been implemented to enhance the final granular attributes. It implies applying non-conventional process parameters, particularly impeller speed, on the granules during the granulation process. The process is named as multi-stage granulation since the granules will pass through different stages of granulation process. The experimental work revealed that by following the multi-stage granulation a noticeable change in the granular attributes has been observed.

In this work, a high shear mixer (Eirich EL1) has been used. Calcium carbonate (CaCO₃) and Polyethylene Glycol (PEG1000) were used as a primary powder and binder respectively. The speed of impeller has been changed in a pulse mode throughout the granulation process from moderate speed to high speed in different intervals of time. Analysis of the produced granules showed that the granular characteristics with the multi-stage granulation were different to that with the conventional granulation process. The granular median size affected clearly during the process as shown in the Figure 1 below. This is due to occurrence of different granulation mechanisms (e.g. growth and breakage) during different stages.

The surface area of the granules has been increased also to some extent after the pulse change in the impeller speed. This increase in the surface area is reflected on the granular dissolution process. The granules collected after the pulse change, were dissolving slightly faster than the granular samples before the pulse change.

Figure 1. Granular shape in the normal and multi-stage granulation.
In twin screw wet granulation process, the binding excipients could be added in two ways: premixed with powder materials before granulation or dissolved in water as a solution. In this paper, the feasibility of using micronized lactose as a solid binder excipient in twin screw granulation process was examined. Different proportions of micronized lactose were mixed with lactose powder before granulation. As a comparison, hydroxypropyl cellulose (HPC) was prepared in solid and liquid phase (i.e., premixed with α-lactose powder and dissolved as solution respectively). Granulation was carried out to investigate the binding potential by studying the effect of micronized lactose and HPC on the granules properties such as size, shape, and surface structure. Due to its small size, micronized lactose was proven to be an ideal alternative as a solid binding excipient to provide strong bonds and produce granules with improved granule size distributions. Furthermore, the binding capacity of micronized lactose was also examined on the compact powder bed where the contact angle, nucleus hardness, and surface structure was studied.
Fine particles in the micron size range or smaller are usually so cohesive that they cannot exist as individual entities and are in cluster form, the size of which depends on the stress history. During handling, transportation or storage, the powder is subjected to mechanical vibration and/or agitation and, as a result of which clumping of particles or "snowballing" can occur even without the presence of any binder. This is due to the attractive van der Waals forces and is usually an undesirable feature, as it is responsible for poor flow behaviour, cohesive arching, segregation of lumps and inducing flaws in products. Nevertheless, the mechanism of auto-agglomeration of cohesive powder has not received due attention and the conditions under which such clusters/lumps form, their size, structure and strength has not been analysed extensively. Previous work [1] has shown that the size of the clusters formed due to vibration can reach an equilibrium value after a sufficiently long time. In the same study, the equilibrium cluster size was found to increase with the vibration intensity. In this work we present a preliminary model to predict the equilibrium cluster size based on two separate energy balances to predict the granule solid fraction and equilibrium size, respectively. Despite some broad approximations, this approach can capture the trend of increasing agglomerate size with the vibration intensity as reported by Ku et al. [1]. The proposed model also identifies the mechanism controlling the growth of the agglomerates as the balance between the cohesive energy of the particles and the disruptive energy of vibration. This study represents a step forward towards a better understanding of the phenomenon.

Layering and coating in fluidised beds are major operations in solids processing. From an industrial point of view, continuous operation is preferred offering the possibility of production under steady-state conditions. Recent modeling and experimental work [1-5] has shown that the stability of steady-states depends on a variety of process conditions, and steady-state operation may not be achievable without process control.

In this contribution, we present an overview on the process dynamics in general and stability of operating points in particular for

- continuously operated cylindrical fluidised beds with internal and external product classification;
- continuously operated horizontal fluidised beds with external product classification;

studying the influence of main operating parameters and the sensitivity of operating points on thermal conditions, highlighting possible routes and challenges for process control. The presentation comprises pilot-scale experimental results as well as simulation studies, obtained from extended population balance models. We provide a critical evaluation of current modeling approaches and their feasibility for the description of process dynamics. Finally, we present ranges of applicability of the different process configurations for a specified product quality (in terms of stable operation and particle size distribution).


8. A HIGH-DIMENSIONAL STOCHASTIC POPULATION BALANCE MODEL FOR TWIN-SCREW GRANULATION

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Twin-screw granulation (TSG) is a relatively new method of continuous granule production and is currently subject to a high degree of research as a viable alternative to batch granulation. TSG systems have shown many advantages over traditional batch production methods such as: production of flow-able granules with high API content; plant footprint reduction; minimisation of API/excipient usage during formulation development and ease of scale-up from development to full production. The versatility of the TSG system allows for variation in the screw element configuration, screw speed, liquid feed rate and powder feed material to enhance desirable features of the granular product during formulation development. This ultimately results in an exceptionally large and complex operating space for the device, necessitating a deep understanding of the underlying process in order to predict, and more importantly, control the properties of the resulting granules.

In this work we present a five-dimensional, stochastic population balance model for twin-screw granulation. The model uses a compartmental approach to encompass changes in particle properties along the length of the screw barrel and allow for different mechanisms to be applied in each specific screw section. The sensitivity of the model to individual rate parameters and the role of specific screw element sections is analysed. The predictive power of the model is assessed through comparison with an experimental dataset.

Twin-screw granulator schematic.
9. A QUANTITATIVE STUDY AND ANALYSIS OF DRUG MIGRATION DURING GRANULE DRYING

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When a wet granule containing a water-soluble active is dried, it is likely that the dissolved active will migrate towards the periphery of the granule as the solvent evaporates. Moreover, the migrated active can deposit itself on the outer crust of the granule upon recrystallization from the solvent. Subsequent powder handling may lead to shedding of this active compound, thereby making the fraction of fine granules super-potent in the drug and consequently lead to losses [1]. In the case of pharmaceutical granulation, a greater extent of drug migration can not only compromise the structural integrity of the granules [2] but also lead to inefficient granulation resulting in content non-uniformity.

This study investigates the extent of drug (active) migration in granules made via high shear wet granulation subject to several factors such as the viscosity of the binder solution, particle size of the excipient and granule porosity. A set of two component systems comprising of Potassium Chloride as a model water-soluble active with Microcrystalline Cellulose PH-101 (mean particle size 50 µm) and Microcrystalline Cellulose PH-102 (mean particle size 100 µm), respectively, were studied at 20% active load in a 3.9 L high shear granulator. In order to eliminate any non-homogeneity due to segregation and difference in wettability of the two compounds, the soluble active ingredient was first dissolved in water or in an aqueous solution of PVP, and this binder solution was then sprayed on the powder bed to carry out granulation. The extent of drug migration and structure of the dry granules was analysed using X-Ray Microtomography (μ-CT).

The dried granules made under conditions of varying binder viscosities, different wet massing times (which allows us to control granule porosity), different drying rates and with excipients having different primary particle sizes were analysed. The extent of capillary migration in the resulting granules was analysed by dividing the μ-CT images into radial cross-sections and quantifying the distribution of the active across these radial cross-sections. Statistical analysis was performed to quantify the extent of aforementioned variables on the extent of migration.

Thus, a comprehensive investigation into the causes of drug migration was carried out in this study to ascertain which factors or combination of factors have the most prominent effect on the extent of migration of a water soluble drug compound during granule drying.

Hence, this study will enable us to identify optimal operating conditions and drying parameters to design robust granule structures and subsequently address content non-uniformity issues in pharmaceutical processes.
Figure 1. μ-CT images of granules prepared under identical conditions, differing only in the viscosity of the binder solution. Granules from three sieve cuts were examined from the two batches. Granules from Batch 1 contained only water and KCl in the binder solution while Batch 2 was granulated using a viscous binder solution with 4 % PVP. The bright white parts represent the active. The granules from Batch 1 show a greater fraction of the active towards the periphery compared to those of Batch 2.


10. PRODUCTION OF GRANULATES OF HYDROXYPROPYL METHYLCELLULOSE LOADED WITH VITAMIN B12 BY WET GRANULATION PROCESS

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Wet granulation is a size enlargement process where small loose powder particles are gathered into larger once (granules), through the use of specific substances known as binders. Key roles in the wet granulation process are played by feed material properties and by operating conditions, influencing the final properties of the product.

In this work, studies on the correlation between product properties and process parameters adopted have been carried out, in order to obtain granules with a good flowability, defined size (0.45mm-2mm), together with an high granulation yield to reduce manufacturing scrap. Moreover, Vitamin B12 is included in the granulated products with the aim to investigate them as model of functional molecule delivery system. The study has been conducted using HydroxyPropyl MethylCellulose (HPMC), biocompatible, hypoallergenic, inert, viscoelastic polymeric powder which was granulated using distilled water as binder. The HPMC powder was placed in a low-shear rate granulator and the binder addition was carried out by an atomizing probe. Finally, granulates were undergone to stabilization by a dedicated dynamic drying apparatus using hot air (65°C) for one hour. The experimental granulation tests were performed by varying three parameters (factors): binder volume, flow rate and impeller rotation speed (rpm). To each factor three intensities (levels) have been associated, defining the minimum, the average, and the maximum value for each of them. Tests were planned through the Central Composite Design method which has allowed to minimize the number of experiments, thus cost and time of experimentation, and to get information about the relationship between granule properties/process parameters. The results obtained show that, only by correctly combining the operating conditions, it is possible to produce granulates with the desired characteristics. For example, a low rpm with a low wetting phase injection time and an high volume of binder may cause overwetting phenomena. The best performance at the operating conditions of 112 rpm, 17 ml/min and 100 ml was found, achieving granulated with 0.45mm-2mm in size, the better flowability (Carr Index 8.28 ± 0.69) and a granulation yield of 75.24 ± 5.45 %. The optimized conditions were used in order to obtain HPMC granulates loaded with Vitamin B12, an active molecule with antioxidant properties, to be studied as model of functional molecules delivery system. Vitamin B12 was encapsulated in the granulated by two different methods: it was dissolved in the binder or premixed with the HPMC powder. The addition of B12 (loading 1%) has shown that no variation of granules properties are achieved (size, flowability and yield values were kept). Dissolution tests were conducted in distilled water to 37°C for a total of three hours and the release of Vitamin B12 was assayed. B12 release studies have revealed that the vitamin was gradually and totally released when the granules manufacturing was performed adding the B12 in the binder phase.
11. PREDICTION OF THE RELATIONSHIP BETWEEN TABLET TENSILE STRENGTH AND COMPACTION PRESSURE USING POWDER COMPRESSION PARAMETERS

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Plasticity of particles is considered to be critical for the development of interparticulate areas of contact during powder compression and hence for the evolution in tablet tensile strength. An indication of particle plasticity can be derived from powder compression data by using the Heckel equation. The compactibility of a powder is often described by the relationship between the tablet tensile strength and the compaction pressure (a strength pressure relationship, $SPR_{exp}$). The prediction of the $SPR_{exp}$ using only compression parameters is challenging. The problem may be overcome by using a hybrid approach that combines compression parameters and a single indication of tablet tensile strength as a reference value. The procedure is based on the assumption that a $SPR_{exp}$ can be simplified into a model consisting of three stages [1]. The objective of this paper was to present the hybrid procedure for the prediction of powder compactibility and to evaluate the procedure.

The needed compression parameters and the $SPR_{exp}$ profiles were derived for six powders with plastic or brittle compression properties and with a variation in particle plasticity. In order to relate the second region of the $SPR$ model to the particle plasticity, an additional parameter is needed. This proportionality factor ($\alpha$) is a priori unknown and was calculated for all powders as the ratio between the width of the second region and the Heckel yield stress. For the investigated powders, $\alpha$ ranged from 2.09 to 4.22. An average value was subsequently used for all six powders in the calculation of the series of $SPR_{pred}$ profiles. The $SPR_{pred}$ profiles thus derived approximated satisfactorily the $SPR_{exp}$ profiles. The approach appears thus to be a material sparing way of characterising powder compactibility.

A comparison between a $SPR_{exp}$ for tablets of lactose and $SPR_{pred}$ profiles using different values of $\alpha$. The measured tablet tensile strength is indicated with an arrow.

12. HOT-MELT FLUIDIZED BED GRANULATION – AN EFFECTIVE LOW-SHEAR METHOD FOR THE MANUFACTURE OF POLYMER PELLETS WITH HIGH ADDITIVE LOAD

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In many applications the need for polymer materials with specific and complex property profiles becomes increasingly important. By using functional additives, essential properties like thermal stability, thermal conductivity, UV-stability, burning behavior or antistatic properties of polymers and polymer-ceramic composites are adjustable. However, these required property profiles cannot be provided by typical basic polymers and are only achievable by loading basic polymer materials with additives. Nevertheless, this functionalization is not directly implementable in most cases. High stresses during processing, e.g. extrusion, can lead to segregation or changes of certain properties of the additives. Therefore, these additives have to be transferred into polymeric carrier systems, protecting the functional particles from damages or degradation by any further processing stresses. Hot-melt fluidized bed spray granulation basically offers an innovative and effective possibility for low-shear embedding of functional additive particles in polymeric carriers.

In this work, the fluidized bed spray granulation of additive loaded polymer melts has been investigated systematically. Beginning with a short introduction of the experimental set-up and general challenges in hot-melt fluidized bed spray granulation, this investigation is giving a detailed insight into the influence of different embedding approaches on achievable additive contents and main process parameters on physical product properties and final application.

REM-Images of polymer pellets with high additive load, obtained by hot-melt fluidized bed granulation.
The control of the wet agglomeration processes of powders depends on the combined contribution of native powders characteristics, energy input, and wetting liquid binder. The objective of this work is to specifically investigate the contribution of the size distribution (d50 and span) of the native particles, on the dimensional and structural characteristics of the agglomerates. Experiments are performed with native semolina particles. The agglomeration process is conducted using water as liquid binder. Several fractions of native semolina with contrasted dimensional properties (d50 and span) are prepared by a sieving procedure. The wet granulation is processed under specific conditions using a low shear granulator at constant blade speed, product load, liquid spraying condition (constant dimensionless spray flux) and residence time. The agglomerates properties are evaluated by the distribution of the measured values of the size, water content and compactness. The mean values and their fluctuations are both taken into account to describe the agglomeration mechanisms.

Whatever the size distribution of the native powder, the mechanisms involved in the agglomeration process are the same but with different importances especially the breakage of agglomerates. We observed specific effects of the span and the median diameter of native powders on the size distribution of the agglomerates. Using small native particles (d50 < 250 µm) improves the homogeneity of the size distribution of the agglomerate bed. Using slightly dispersed native particles (span < 1.0) leads to a better uniformity on the size distribution. We demonstrate that the conditions to obtain a population of agglomerates with a narrow size distribution depend on the ratio between the water droplet diameter (d50drop ~ 250 µm), and the median diameter of the native particles. This diameter ratio is considered as a process parameter. We propose to build a modified dimensionless spray flux number by incorporating this diameter ratio. The nucleation step is specifically described by this new dimensionless number.
14. SOME SPECIFICATIONS FOR THE SUSTAINABLE-DESIGN OF THE AGGLOMERATION PROCESSES OF FOOD POWDERS

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Over the 15 last years, many scientific works have been devoted, on the identification and understanding of the hydro-mechanical paths of reactive powders during the agglomeration process. However, from the grain and drop scales, to the reactor scale, the variability of the raw materials associated with the differences between various technologies (low or high shear mixer, kneader, fluidized bed…), induce a high degree of complexity which makes it difficult to define a unified and generic framework. It is in particular difficult to build a coherent representation which could lead to define eco-efficient and energy consuming yields. The objective of the present work is to propose the basis of a unique continuous description of the agglomeration mechanisms when using using different technologies of low shear mixer under different operating conditions (water content, mixing speed, and residence time).

The wet agglomeration mechanisms are studied at the agglomerate scale by considering evolutions of size, water content, and compactness of the wet agglomerates. Mean values and their fluctuations are both taken into account to describe the impact of the process on agglomeration. We demonstrate that agglomerates are saturated whatever the processes and operating conditions. The evolution of the size distribution of the agglomerated structures (nuclei, agglomerates, and dough pieces) with compactness shows a continuous growth process associated with the expansion of their internal structure. The understanding of their hydrotextural states suggests similar mechanisms of structuration. These mechanisms deal with (i) classical growth of associated particles to nuclei, then nuclei to agglomerates, and percolation to local paste state (dough pieces), and also (ii) fragmentation of dough pieces into a specific population of small saturated clusters, which are able to interact with nuclei. The quantification of each population gives a tool to describe the role of the process and the contribution of the energy input. It is possible to link different processes under low shear conditions or using high shear mixer to generate agglomerates with same specific functionalities.
15. THE EFFECT OF TWIN SCREW GRANULATION ON THE TABLETABILITY OF PHARMACEUTICAL EXCIPIENTS

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Granulation is mainly used to solve powder handling problems. However, granulation can have a negative influence on powder transformation into a tablet, i.e. tabletability [1]. In the literature, several researchers have investigated the mechanisms of loss of tabletability due to dry granulation.

Limited work has been done to examine the mechanisms of loss of tabletability due to wet granulation using high shear mixer. With the increasing utilisation of twin screw granulation (TSG) in the pharmaceutical industry, there is a need to study the effect of TSG on the tabletability of wet granulated materials.

The aim of the work is to examine the effect of continuous granulation using TSG on the tabletability of wet granulated materials. A range of pharmaceutical excipients namely, microcrystalline cellulose, mannitol and calcium hydrogen phosphate were granulated using a 16mm TSG (Euro lab 16 TSG, Thermo Fisher Scientific, Karlsruhe, Germany). Granules were produced at a variety of shear stresses by using a range of screw speeds and screw configurations. Granule and tablet properties were characterised and it was found that TSG has an impact on the tabletability depending on the mechanical properties of the granulated pharmaceutical excipient.

16. DYNAMICS OF PARTICLE-WALL COLLISIONS: INFLUENCE OF WETTING CONDITION

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Granulation processes are characterised by intense contact between particles and particles with the apparatus walls, where often a liquid is present on the surfaces in form of droplets or liquid layers. Although granulation is widely used in industry, until now there exists no complete description of the collision dynamics of wet particles and walls.

Therefore, in this work the influence of the liquid on dynamics of wet particle-wall collisions is investigated via coefficients of restitution. The coefficient of restitution characterises energy dissipation during a collision and is defined as the ratio between rebound and impact velocity. It depends strongly on the collision parameters (such as collision velocity and angle), particle properties (size, roughness, deformation behaviour) as well as on the properties of the liquid (viscosity, layer thickness). In most literature regarding collision dynamics of wet particles, a target plate was covered by a liquid layer before the collision. However, the large amount of liquid, which is evenly distributed over the target plate might have an influence on the collision dynamics. Therefore, during this work the particle was wetted before colliding with a dry plate by letting it fall through a liquid layer, which is distributed inside a ring (see figure). Oblique collisions could be performed by angling the target plate. Ultimately, the results for wet plates were compared to those with wet particles.

Normal collisions showed no difference if the wall or the particle were wet before the collision. However, during oblique collisions some differences could be found. Mainly, the tangential coefficient of restitution was smaller for a wet wall compared to a wet particle impacting a dry wall.

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Schematic representation of the experimental setup and example for particle movement during wetting of the particle and collision with a dry wall.
17. EXPERIMENTAL AND NUMERICAL INVESTIGATION OF WET PARTICLE WALL-COLLISIONS

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Agglomeration and granulation processes are characterised by intense contact between wet particles and particles with the apparatus walls. The liquid, which can be present in form of droplets or liquid layers on the surfaces, has a fundamental influence on collision dynamics and adhesion of particles. However, until now there exists no complete description of the collision dynamics of wet particles and walls.

Therefore, in this work collision dynamics are analysed experimentally by evaluating high-speed images of actual particle-wall collisions as well as numerically by solving force balances of such collisions. The coefficient of restitution (CoR), which is defined as ratio of rebound to impact velocities and therefore, gives information about the energy dissipated during the collision, is used to compare both results. The coefficient of restitution depends strongly on the collision parameters (such as velocity, initial rotation, angle), particle properties (e.g. size, deformation behaviour) as well as on the properties of the liquid (layer thickness, viscosity).

Normal and oblique collisions are investigated including rotation of the particles. The normal component of the coefficient of restitution was found independent of collision angle, initial rotation and surface tension experimentally, but strongly dependent of normal collision velocity, layer thickness and viscosity. The tangential coefficient of restitution in comparison appears to be influenced by initial rotation and collision angle, but independent on normal collision velocity and viscosity. Comparing experiments and numerical investigations via force balances, overall, good agreement was found.

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Figure: Left: Example for particle movement during collision of a dry particle and a wet wall; right: Experimental and numerical coefficient of restitution for a glass particle colliding at different velocities with a glass plate covered by a 400 µm thick liquid layer of different viscosities.
In this work, Computational Fluid Dynamics (CFD) modelling has been used to simulate the behaviour of fluidized beds of Geldart D particles, relevant class of particles for several fertilizer granulation processes. The gas phase and the solid phase are both treated as interpenetrating continua, and the particles rheology is described by means of the Kinetic Theory of Granular Flow (KTGF). OpenFOAM software was used for the simulations. Numerical results for 2D planar and 2D axisymmetric simulations are compared with experimental data from a batch pilot-scale fluidized bed.

The effect of the air velocity and particle size on the behavior of bed expansion is studied. Characteristics of the bubbling regime are also analyzed by means of the erupting bed surface. It is confirmed that the CFD model is able to capture the gas-solid flow features of the fluidized bed of the studied type of particles.

Contour plot of particle volume fraction.
HYDROPHOBIC/HYDROPHILIC STATIC POWDER BEDS:
COMPETING HORIZONTAL AND AXIAL SPREADING MECHANISMS OF
A SINGLE DROPLET

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The competing spreading mechanisms of a single liquid droplet impacting on static powder beds of varying hydrophilic and hydrophobic compositions has been investigated. The drop impact velocities and viscosities of different binders namely water, polyvinylpyrrolidone (PVP), hypromellose (HPC) and starch were also considered. By using a high-speed video camera, the droplet spreading behavior on static powder bed compacts was captured, then the resultant nuclei morphology was analyzed. Results show that the axial \( (d_a) \) droplet spreading mechanism is highly dependent on the interfacial tension between the solid and the liquid droplet. The \( d_a \) in this case is defined as the length the droplet travels axially into a powder bed. Whereas, the horizontal \( (d_h) \) droplet spreading mechanism, the length the liquid droplet travels horizontally across the powder bed showed a high degree of dependency on the binder viscosity. The experimental data indicates that this transitional liquid droplet spreading behavior is evidence of the transportation of a liquid droplet occurring increasingly via site percolation theory with increase in formulation hydrophobicity. Understanding of single droplet spreading mechanisms provides a basis to select the optimal binder for granulation to form more uniform and robust granules when using hydrophobic formulations.
Fluidized bed spray agglomeration is applied in many industries, e.g. the pharmaceutical industry, food industry and agriculture, to produce free-flowing and dust free particles. In fluidized bed agglomeration the particles are fluidized using a hot gas, e.g. air. This causes the particles to collide with each other leading to the formation of liquid bridges. Due to simultaneous drying the liquid bridges are transformed into solid bridges. However, it is also possible that a liquid bridge breaks due to mechanical stress before drying is completed. In this case no agglomerate is produced. Instead, two partially wetted single particles exist, which may undergo further agglomeration events. This effect (contact liquid dispersion) may influence the kinetics of an agglomeration process.

In the literature the influence of contact liquid dispersion on wetting of a particle bed in a rotating drum has been investigated in the frame of a DEM simulation [1]. In the present study, contact liquid dispersion will be implemented into a stochastic process model of fluidized bed spray agglomeration. Using this model the influence of the contact liquid dispersion on the wetting of the particle bed and on the kinetics of the agglomeration process will be investigated.

This study focuses on the role that various elements (conveying-type elements (CE-type), kneading elements (KE) and tooth mixing-type elements (TME-type)) play in the reduction of fines, which are defined as < 150 microns granules in twin screw wet granulation (TSG) when using increasing amounts of hydrophobic powder in the formulation composition. Further, this work attempts to rationalize the positioning of the various screw elements along the barrel by studying the granule size, granule porosity, liquid binder distribution, residence time (RT) and residence time distribution (RTD) results. The length of the screw elements was kept constant to guarantee constant and comparable mixing quality.

It was found that CE-type elements promoted poor mixing through concentration of activity in the intermeshing region of the twin screw which resulted in large agglomerates being formed together with a large amount of < 150 microns granules. At increased formulation hydrophobicity, the distribution of the liquid binder droplets using the CE-type elements became unachievable forming liquid marbles ‘solid particles spreading around the liquid droplet’. The order of superior cross-sectional mixing behavior across the barrel channel width was observed to be CE < KE < TME, particularly with increase in formulation hydrophobicity. This was due to progressively improved liquid distribution with increase in material residence time which resulted in fewer production of < 150 microns granules and greater extent of granule formation with that order of elements.
SCALE DOWN OF AGITATED FILTER DRYING OF ACTIVE PHARMACEUTICAL INGREDIENTS

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The most common mode of drying is agitated drying as it increases the rate of production by enhancing heat and mass transfer but it exposes the API to attrition and agglomeration. In this work, attrition is defined as the surface wear and fragmentation of particles whereas agglomeration is the natural phenomenon of particles sticking to each other or to solid surfaces because of binding mechanisms [1,2].

In the past, the smallest scale testing of Active Pharmaceutical Ingredients (APIs) in an agitated dryer was being done on the 100 ml scale. We have developed a lab scale of 50 ml. The engineers & scientists are now able to use the proposed protocol and new equipment to have a good grasp of what kind of phenomena they can expect when drying at a larger scale. Though most of the work was done on model compounds: Paracetamol, Caffeine, Mannitol, and Vanillin, I have done experiments with Novartis compounds to test the reliability of the new protocol and equipment.

In conclusion, the new Miniature Agitated Filter Dryer that has been built shows promise in being able to be used for better understanding of agitated drying of APIs by obtaining data at a smaller scale of 50 ml. The key parameters to control during investigative studies, as confirmed in literature and empirically, are as follows: particle properties, agitation protocol, solubility and moisture content (%LOD).


Wet granulation is typically achieved by one of three kinds of processes: high shear, twin screw, and fluid bed granulation. These three avenues have several key mechanistic differences. Agglomeration, breakage, and consolidation drive high shear wet granulation processes, while fluid bed granulation processes are also influenced by drying. In contrast, agglomeration plays a minor role in twin screw granulation processes, which are driven by drop nucleation, breakage, and layering. In this work, a mechanistic population balance modelling framework is presented and applied to twin screw, fluid bed, and high shear wet granulation processes.

In order to apply these tools to real processes, the models must be calibrated and validated with experimental data. Model validation is not well-established for wet granulation processes, and the large number of unknown kinetic parameters presents a significant obstacle. In this work, strategies for model validation are developed based on the mechanistic understanding of the complex relationships between critical process parameters and product attributes. This fundamental understanding is used to decouple key mechanisms of wet granulation processes and design targeted experiments that are rich in information and minimize the data requirements of the model. Case studies are presented that demonstrate model development and validation for fluid bed and twin screw granulation processes. Once validated, these models can be used to improve process design and performance and achieve targets for product attributes.
MICROSTRUCTURAL CHARACTERISATION OF FUNCTIONALISED CALCIUM CARBONATE TABLETS BY MEANS OF TERAHERTZ MEASUREMENTS

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The compaction of powder is typically used to manufacture pharmaceutical tablets consisting of an active pharmaceutical ingredient (API) and several different excipients. Most excipients are considered to play an inert role during drug delivery but are crucial in defining the ease of tableting, generally in respect to flowability, compressibility and uniformity of API dose distribution within the tablet. However, novel excipients are entering the market to enhance solubility of the drug by having a high porosity and thus providing a rapid liquid uptake. Such a novel excipient is functionalised calcium carbonate (FCC, Omyapharm®, Omya AG) formed in a process whereby the surface of calcium carbonate particles is etched and then re-precipitated to create a highly porous, high surface area material. Compacts of this excipient have a discretely separable bimodal pore size distribution, consisting of larger inter-particle and fine intra-particle pores. Five sets of FCC tablets with a target porosity of 45% to 65% in 5% steps were prepared and characterised using terahertz time-domain spectroscopy (THz-TDS) and terahertz pulsed imaging (TPI). THz-TDS was employed to derive the porosity and a structural parameter S of the FCC samples. Considering the pore network as a combination of pore components in series and in parallel assembly, the structure parameter S is related to the prevalence of in series and in parallel pore components [1]. The high acquisition rate (15 Hz) of TPI enabled the analysis of the rapid liquid penetration of water in the FCC tablets [2]. The results clearly indicate that the liquid ingress (several seconds) is linear t-dependent (inertial Bosanquet regime) for short timescales before it follows Darcy’s law (i.e., √t-dependent). Furthermore, the penetration kinetics were related to the porosity and the S parameter measured by THz-TDS of each tablet. This revealed that the initial liquid penetration velocity correlates linearly with the porosity and the permeability of the tablets. This study highlights the strong impact of a tablet’s microstructure on its liquid penetration kinetics and thus on its disintegration behaviour.


Fluidized bed spray coating is applied in food and pharmaceutical industry and facilitates the design of various coated particulate products by fluidisation of core material, on-spraying of liquid mixtures, convective drying and solidification of coated substances, simultaneously. The ability of defining diverse product properties such as particle size distribution or coating layer thickness distribution is one of the advantages which are of peculiar interest for coating processes. What is more, the features of granules can be supplemented with further qualities such as taste masking for granular food products, higher mechanical stability due to less breakable coating materials or the definition of certain required drug release rates by coating of particles containing active pharmaceutical substances.

For encapsulation of several coating materials by continuous multi-stage fluidized bed spray-coating with inter-connected air classifiers, the control of a required coating layer mass distribution is needed in order to ensure presupposed product quality features. To achieve this, it is important to yield the acquaintance about the process behaviour for a single stage regarding particle size distribution of separated coarse particles and fluidized bed mass representing product quality and process stability respectively. For describing the one-stage fluidized bed spray coating a particle size distributed system is assumed as well as a two-zone population balance model including particle size selective separation step is deployed and presented in this contribution. Employing this model used in former research (e.g. [1]), the influence of several model parameters on product quality properties and process stability are investigated and discussed in the present study. It is focused on particle size distribution of product discharge and the temporal evolution of bed mass. Furthermore the simulation results for various model parameter settings using different control methods are compared with each other.

26. EFFECT OF GRANULATION ROUTE ON TABLET DISINTEGRATION

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In the manufacture of pharmaceutical products, a granulation step is commonly used for adjusting powder properties before undergoing compression during the tableting step. In this work, wet granulation is considered. The active pharmaceutical ingredient (API) is mixed with excipients, and following the addition of a binder and depending on the granulation parameters (main impeller speed, chopper speed, etc.) produces granules with a specific size distribution, composition and inner structure (arrangement of primary particles within granules). These properties jointly determine the dissolution properties, which result in different release profiles of the API from granules prepared under different processing conditions even if their composition is identical [1]. An open question is, to what extent granule properties are projected to tablet properties and how the applied tableting pressure affects the dissolution properties of final dosage form [2].

The aim of this work is to investigate the transferability of granule properties into tablets. This is a non-trivial task where granules with different individual dissolution behaviour, produced at different Froude numbers, were subjected to low and high applied tableting pressures in order to challenge the hypothesis that a high compaction pressure should crush the original granules while in the case of lower compaction pressures the structure of the original granules could be at least partially preserved. The granules were described by PSD, bulk density and dissolution profiles. The tablets hardness was measured on a Sotax HT 1 and extended mechanical testing provided load-displacement characteristics from a needle penetration test on the Texture Analyzer. In vitro dissolution tests were conducted in pH 4.5 and 6.8 buffer and complemented by advanced imaging approaches [3]. A high Froude number implied more rapid dissolution for tablets produced at low applied force, while applying a high tableting force resulted into slower dissolution of tablets in comparison with tablets compacted from granules produced at low Froude numbers. These results pointed out the different compressibility of granules prepared at different Froude numbers, and the non-trivial interaction between structure formation during the granulation and tableting steps when manufacturing pharmaceutical products. In line with the Quality-by-Design (QbD) philosophy, stable ranges of Froude number in combination with given tableting force, where the final dissolution characteristics are robust with respect to variations of operating parameters, were found.


Coating thickness of pellets is an important quality attribute that influences the desired coating functionality. Based on a simplified model of the coating phenomenon, the variability in cycle times and the shading effect of pellets in the coating zone are two fundamental aspects that lead to the overall variability of the coating thickness of pellets. Both phenomena can be addressed separately.

A tracer photoluminescence detection system for evaluation of pellet cycle times was developed and utilized in a lab scale Wurster coater. The system was mounted on top of the Wurster draft tube, facing the annulus region of the Wurster coater. The output voltage of the detection system was sampled with high frequency in order to detect short voltage spikes, caused by the tracer pellet passing the excitation and detection zones of the system. The time span between consecutive voltage spikes was interpreted as cycle time. Tracer pellets were representative for evaluated population of pellets in terms of size and density.

The influence of pellet size and load, fluidizing air flow rate, partition gap, relative air humidity and air filter material type on the pellet cycle time distribution was studied. The medians of the measured cycle time distributions ranged from 1.8 to 7.6 s and the corresponding mass flow rates ranged from 132.4 to 551.7 g/s. Based on typical pellet coating thickness variability data, obtained for coating processes of pellets in the same lab scale equipment, the contribution of the variability of the cycle times to the overall variability of the coating thickness of pellets was evaluated.
INVESTIGATION OF THE DYNAMIC BEHAVIOUR OF THE SPRAY GRANULATION IN A CONTINUOUSLY OPERATED HORIZONTAL FLUIDISED BED

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

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

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Naturally occurring structural materials are usually composites with very high filling degrees on hard constituent. In recent years structure and properties of biological materials have been studied in detail. But it has not been possible to reconstruct this structural design. In this contribution we present a process for the fabrication of highly filled composite materials by using of the spouted bed spray granulation process.

Spouted bed granulation offers many advantages for the design of composite materials. In this investigation fine particles could be uniformly spouted, and optimal properties for further processing to bulk materials can be obtained by means of granulation. For this a hybrid spouted bed with horizontal gas inlets was designed, which has a small prismatic process chamber with adjustable inlets and a high conical-cylindrical relaxation zone. The thickness of the polymer layer is adjusted by a two-fluid nozzle. The adjustment of the thickness of the polymer layer is very important to fabricate composites of adjustable filling degrees. After granulation the particles are assembled to a composite material by means of warm pressing. For determination of mechanical properties 4-point bending-tests were carried out. In the current study copper particles were used as model materials to investigate the influence of aspect ratio on mechanical properties of composites. Also electrical properties of such composites were studied. For the optimisation of the granulation process coupled CFD-DEM simulations of the spouting process are carried out and results of the simulation and mechanical tests will be presented.

SEM of copper particles before processing (left) and SEM of copper-polymer agglomerates after the processing in the spouted bed (right).

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Increasing of quality of different dispersed materials can be reached with using a granulation in horizontal high-speed cylindrical granulators. These apparatus are widely used for granulation of powder material in production detergent, fertilizers and tablets.

The aim of this work is the modeling of the process of granulation in high speed horizontal granulator and experimental investigating.

Preliminary experiments show that the process of granulation is a result of both agglomeration of fine particles and disintegration of the formed granules. In continuous operation of a high-speed granulator, granules are actively formed in the region of binder feeding owing to agglomeration of fine fractions. As the dispersed material is transported along the apparatus axis, the amount of the free binder decreases, and the agglomeration decelerates. The effect of the granule disintegration as a result of collisions with rotor pegs or of the action of high shear stresses, on the contrary, becomes noticeable. Mathematical model of this process were based on kinetic equation that describes agglomeration of the small particles and disintegration of granules.

Use of the equation allows determination of the dynamics of the particle weight(size) variation in the course of transport of the material being processed under the conditions of competing action of two processes: coagulation and disintegration. For a continuous steady-state granulation process, the explicit form of the dependence allows determination of the cross section of an apparatus in which disintegration starts to prevail over coagulation. For a batch process under the conditions of ideal mixing, from the explicit form of the dependence one can readily determine the time moment when the dynamic equilibrium between the coagulation and disintegration processes is attained (See Figure 1).

Figure 1. Dynamics of variation of the mean granule weight at different rotor rotation rates.
The oral drug delivery system using bilayer (or multilayer) tablets have become more commonly used in therapeutic strategies. One of the most common problems associated with bilayer tablets is the insufficient interfacial strength between the layers, which is the main cause of the product failure. In the study, the tensile strength of microcrystalline cellulose (MCC PH 102) bilayer tablets made at different manufacturing conditions was investigated.

Three testing cases were considered:

Creating the tablet layer interface with different curvatures using flat, convex and concave punches. The curved punches were used with two different curvatures, the same curvature radius (17.6 mm) but different curvature depths (1.25 and 1.30 mm).

Changing the water content in the bilayer tablets. The powder storage humidity was changed to produce MCC powders with certain water contents (i.e. 4.0%, 6.2% and 10.9%).

Varying the particle size of the powder used in first layer. The commercial powder was sieved using a 90 μm mesh to produce coarse powder (i.e. d50=105 μm) and fine powder (i.e. d50=76 μm).

Direct tensile tests were performed to measure the interfacial strength. According to the testing results, it has been found that the interface shape, the water content in powder and the first layer particle size affected the interfacial strength significantly. It is shown that the interfacial strength can be improved by using larger particle size in first layer, optimising tablet interfacial curvatures with curved punches (i.e. either convex or concave punches) and properly controlling the water contents.
High shear wet granulation is one of the most commonly used methods for the particle size enlargement in pharmaceutical industry. In this process different phenomena occur simultaneously affecting the final granule properties. Their evolution is related to two key aspects: the strength of the wet mass and its deformation. Indeed, as proposed by Ivenson et al., these two parameters are used to draw growth regime map of the granules, an useful instrument to describe and to predict the evolution of a granulation process. The drawback of this map is that it is necessary to estimate numerous parameters (wet granules porosity or collision velocity for instance) or to perform complex characterizations (e.g. measure the wet granule strength in dynamic conditions). Consequently, the purpose of this study was to perform a complete characterization of the rheological behavior of the wet masses by using a mixer torque rheometer (MTR3, Caleva, UK) in order to easily and quickly describe their behavior during the granulation process and correlate it to the different growth mechanisms.

Formulations containing cellulose microcrystalline (MCC) as diluent and different amounts of xanthan gum (XG) as binder were selected for this study, where XG was added both as liquid and solid dispersions. All the formulations were initially characterized by liquid-solid contact angle and drop penetration time evaluations. The amount of liquid (water or XG aqueous dispersion) necessary for granulation experiments was determined by the mixer torque rheometer using the multiple addition method. In order to evaluate the rheological behavior of the wet masses, torque value was registered over the time using the variable mixing time method. Granulation experiments were performed in order to verify the ability of MTR3 to predict the amount of liquid binder and the wet granules were characterized by measuring their consistency. Dried granules were then subjected to sieve analysis, crushing test and image analysis. Finally, material exchange experiments monitoring the dispersion of a colored tracer among the wet granules were performed.

Results have shown that the rheological characterization of wet mass could represents a useful tool to predict the behavior of the wet mass during the granulation process and the final granule properties. The consistency values gave a fast and easy measure of the wet granule strength and correlated well with the results obtained in the material exchange experiments.
AN INVESTIGATION ON THE DISSOLUTION QUALITIES OF FOAM GRANULATED PRODUCTS

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The worldwide home care industry makes widespread use of granulated laundry powders which must be highly soluble and dissolve rapidly to induce an effective wash cycle¹. The morphology of these granulated powders influences their dissolution rate. Binder addition methods affect the final properties of granulated products²-⁵. Foam granulation is a method of granulation in which a foamed binder is used to induce agglomeration. The method may provide added advantages such as increasing wetted area per added liquid mass, reducing saturation of the powder bed and enhancing dissolution rate through advantageous granule structures or better bulk size distribution.

In detergents binder is pre-neutralised with a basic solution to induce partial neutralisation before being completely neutralised in a sodium carbonate bed to create surfactants, introducing excess water. Investigations into foam granulation may be of interest to laundry powder manufacturers as a means of reducing the water requirements of their process by encouraging complete neutralisation of the acidic binders without pre-neutralisation. Three separate binder addition methods (spray addition, drop addition and foam addition) were trialled using a model lactose and microcrystalline cellulose (MCC) based formulation to assess the effect of foam granulation without chemical reaction on size, granule structure and dissolution behaviour. Dissolution kinetics were measured via UV-visible spectrophotometry and granule disintegration and dissolution was followed using Focused Beam Reflectance Measurement (FBRM). The granule morphology was analysed using Scanning Electron Microscopy (SEM), X-Ray Tomography (XRT). Bulk granule properties of bulk density and size distribution were also measured. It was observed that foam granulation produced smaller granules at the same liquid level, with a different morphology (see Figure 1) but the dissolution kinetics of the final granules were unaffected by the binder delivery method.

Figure 1: Foam (left) vs Standard Granulation (right) both observed structures after 30 min wet.


This study looks at the extrusion/spheronization process as a method for preparing multiparticulates. Formulation and several processing parameters were evaluated through a design of experiments. The goal is to understand the impacts on particle size and distribution, sphericity, friability and yield of the target bead size as compared to a standard sugar sphere product.

Four factors were studied in a model robust, response surface design with 27 runs using DOE Fusion Pro. The four factors were, binder level, water level, spheronization speed and spheronization time. Metoprolol, a common MP product, was chosen as a model drug for this study. A drug loading of 40% was selected due to the high solubility of the drug. Starch 1500®, partially pregelatinized starch, was used as the binder in the formulation and varied from 1 – 7%. The balance of the formulation was 50 micron microcrystalline cellulose. Batches, 750g, were wet granulated in a Glatt VG 25M high shear granulator with a 5L bowl. Water was sprayed into the granulator with a pneumatic nozzle and a pump. The wet mass was then extruded through an LCI MG-55 extruder with a 1mm x 1mm dome die. The extrudates were then spheronized with different spheronization speeds and times with an LCI QJ-400TG spheronizer. Resulting beads were then dried in a Glatt GPCG-3 fluid bed dryer. Batches were analyzed using a Camsizer P4, dynamic image analyzer and then sieve cut with 16 and 20 US mesh screens representing the target bead size. The yield of target size particles was then determined. Batches were again analyzed with the Camsizer to evaluate size and shape. Each batch was then tested for friability using an Erweka GTA 120 friability tester. Select batches were evaluated with an optical microscope and tested for dissolution to determine drug release variations.

A wide range of results was seen in this study. Due to the high quantity of soluble API, water level was the most significant variable impacting the results. Sphericity and yield of target particles showed some of the widest spread. Sphericity ranged from very round beads of 0.961 to irregular shaped rods of 0.846. To achieve high sphericity, higher spheronizer speed and longer spheronization time is required. This also resulted in particle agglomeration which drastically reduced the yield of beads in the target size range. The run showing the maximum sphericity produced only a 24% yield. Friability was mainly impacted by water level; higher water levels produced less friable beads.

The model formulation showed high sensitivity to the water level used in the granulation phase of the process and impacting the quality of the resultant sphere properties. High sphericity and low friability can be obtained from the extrusion spheronization process but the parameters used to produce product in the best ranges, may result in significant waste in the process by not meeting the appropriate target size. Compromises in the key responses must be made to balance the key response outputs. Utilizing sugar spheres rather than the extrusion/spheronization process can result in more consistent and robust multiparticulates. The next phase of this study will evaluate drug release variation after coating the beads with a barrier membrane coating compared to a drug layered sugar sphere.
Fluidized bed coating is widely used in pharmaceutical, chemical and food industries for particles production. The bottom-spray is one of the best choices for particle coating as it can produce a superior film compared with other coating strategies.

In this research, an electrical capacitance tomography (ECT) sensor with 12-4-8 combined electrodes was designed and used to monitor the coating process in a lab-scale Wurster type fluidized bed. The measurement was conducted synchronously both inside and outside of Wurster tube, i.e. coating region and annular region, to achieve a complete monitor of fluidized bed process with Wurster tube. Key process parameters, including moisture, cross-sectional particle concentration, averaged particle concentration in the chamber and domain frequency spectrum of the fluctuations in the chamber, were analysed based on the measured capacitances and reconstructed images. Different stages in the coating and drying process were revealed based on the reconstructed images and capacitance signals. Experiment results indicate that ECT technology is an efficient tool for pharmaceutical fluidised bed process monitor.

Figure 1. Averaged particle concentration in a coating process.
EFFECT OF MOISTURE CONTENT ON FLOWABILITY OF PULVERIZED COAL

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Reliable feeding of pulverized coal into the gasifier is of great importance for the pressurized entrained-flow gasification process. Moisture content and corresponding interparticle force can strongly affect the flowability of pulverized coal, making it worthy of study. In this paper, flow properties of pulverized coal in terms of angle of repose, compressibility, shear behaviours and flow energy etc. were measured using a PT-X powder flow tester and a FT-4 powder flow rheometer, respectively. With respect to the typical flow indicators, critical moisture contents were defined and the flow characteristics of pulverized coal in each region were analyzed and compared. Further, a combination of a continuum approach and a particle–particle approach to describe the multi-scale nature of the mechanical properties of pulverized coal were carried out. The interparticle forces of pulverized coal with different moisture contents were predicted using the microscale approaches of Rumpf equation. This result was compared with that determined from the Laplace–Young equation which described the capillary condensation between neighbouring particles and used to estimate the capillary forces. Finally, effect of moisture content on flowability of pulverized coal was obtained by revealing the interrelations between flow properties and interparticle force of pulverized coal with various moisture content. The results indicated that different types of moisture content were formed for the wet pulverized coal, and each type could have different contributions on the flowability and interparticle force of pulverized coal.
The breakage of granules is an inevitable phenomenon during the shaping of a pharmaceutical compact, and hence of central relevance for the compaction procedure. However, the aforementioned phenomenon can, most likely, not be fully assessed through simple uniaxial crushing tests, since the forces exerted on an individual granule in a powder bed varies significantly with its local environment (i.e. neighbouring particles and contact with die walls).

In this work, we experimentally investigate the dependence of the compressive tensile strength on the loading conditions for four different granule types in the mm-scale, all based on microcrystalline cellulose (MCC). Apart from uniaxial compression, several triaxial loading cases were studied. For this purpose, a triaxial testing apparatus previously developed at our lab was employed [1]. In addition to the mechanical measurements, the breakage patterns of the investigated granule types were visually examined using X-ray micro-computed tomography (micro-CT).

Whereas granule breakage generally was observed when the granules were subjected to uniaxial compression, the granules tended to remain largely when compressed hydrostatically.

A NEW PROCESS FUNCTION FOR THE DESCRIPTION OF THE POWDER COMPACTION PROCESS

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Tablets are the most important pharmaceutical dosage form and, thus, various investigations focused on the tableting process in the past decades. Nevertheless, the formulation and process development is still empirical because of a missing physical process understanding. Certainly, one reason is the high number of influencing parameters, such as compaction parameters and the deformation behaviour of the various raw materials. The influencing parameters affect the compaction process itself as well as the mechanical and structural properties of the final tablets.

In general, different deformation mechanisms occur during powder compaction. The most important ones are particle rearrangement, elastic and plastic deformation and fragmentation of single particles. However, also an increase in solid density contributes to the increase in powder density. These mechanisms appear in parallel, whereby the proportions of the single mechanisms differ in dependence on the used materials and process parameters. All different deformation mechanisms contribute to the volume decrease during powder compression, so that the powder compression process can be described by the relation between volume or porosity and compaction stress, i.e. compressibility \cite{1}. Various mathematical models for the description of this relation were developed, such as the models of Heckel and Kawakita \cite{2,3}. Nonetheless, these models are mostly empirical and describe often only a part of the compaction process.

In this work, a new process function based on mechanistic considerations was developed. This model describes the whole compression process and, therefore, takes particle rearrangement, elastic and plastic deformation, enlargement of solid density and particle fragmentation into account. The physical explanation of this new model was supported by experimental investigations. In addition, the compressibility of various pharmaceutical materials was investigated by in-die analysis using the compaction simulator Styl'One Evolution (Medel'Pharm, France) and the results were used for the review of the validity of the new model. The new process function enables the prediction of the compressibility based on material and process parameters and, thus, reduces the empiricism of the formulation and process development. Additionally, this model should be transferable to other compaction processes, such as roller compaction, due to its mechanistic basis.


INVESTIGATION OF TABLET DISINTEGRATION USING AN ON-LINE PARTICLE IMAGING APPROACH

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In the pharmaceutical industry the behaviour of a solid dosage oral tablet is studied in vitro before it can be considered as viable drug delivery system in vivo. Tablet disintegration and dissolution are the key processes which are analysed to determine the bioavailability of the active pharmaceutical ingredient. However, the standard USP testing methods used to analyse tablet disintegration are not probative, and only determine whether or not the tablet disintegrates in the required time frame. Little further information is gained about the various processes and mechanisms which occur at the initial stages and during tablet disintegration. The aim of the present research is to gain a better understanding of tablet disintegration using a particle imaging approach. A purpose-built flow cell was employed which is capable of on-line observation of tablet disintegration, and which is able to visualise and measure the change in tablet area and rate of particle release. This additional information could facilitate a better understanding of tablet behaviour, and consequently lead to more proficient tablet design.

Excipient materials were roller compacted using a lower and higher pressure (20 and 100 bar, respectively) and tablets were produced by compressing the consequent granules at varying tableting loads. For this study mannitol, a brittle and soluble material, and microcrystalline cellulose, a deformable and insoluble material, were investigated at varying ratios. It was found that tableting load has a greater impact on the disintegration behaviour than the roller compaction pressure.

Thank you to AstraZeneca for their funding and support of this project.
Spray drying is widely applied in many industries, such as pharmaceutical, food, detergents, polymers, to convert liquids in solid particles [1]. However, it still requires continuous innovation in order to provide more sophisticated particles, which are difficult to design by using only empirical approaches. Indeed, several formulation and process variables have to be carefully selected to achieve the desired properties [2,3].

In this context, a steady-state mathematical model for a co-current spray dryer is developed to give a more phenomenological insight in the production of inhalable particles. The model includes mass and energy balances for both particulate and gaseous phases. The gas flow and droplets velocity patterns are provided by CFD simulations. Particularly, and as a model inhalable compound, the spray drying of ciprofloxacin (CIP) aqueous solutions is studied.

Several experimental data, obtained in a Mini-Spray Dryer B-290, BUCHI, were available (CIP concentration: 10-50 mg/mL, drying air inlet temperature: 110-180 °C, liquid feed flowrate: 3.0-6.0 mL/min and atomization air flowrate: 473-670 L/h). In addition, droplet size measurements were carried out by using laser diffraction. The effect of the binary nozzle operating conditions (atomization air and liquid feed flowrates) on the droplet size distribution was analysed and a correlation to predict the mean Sauter diameter was established.

The experimental data are used to fit and validate the proposed model. The validated model is used to perform parametric studies in order to evaluate the effect of the main process variables on the final product properties (e.g., particle size and density, powder moisture content) and to optimize key powder attributes for pulmonary administration.


The Fast Multi-pole Boundary Element Method (FMBEM) is a new computational method derived from the Boundary Element Method, but with greater computational efficiency. It is computationally more expensive than DEM but DEM requires some features of particle-particle and fluid-particle interactions to be known a priori and FMBEM can capture them from first principles even for non-spherical particles. The features include the ability to account for (a) liquid interface merging during powder wetting and agglomerate densification, (b) liquid junction rupture during agglomerate dilation/breakup for any saturation state and (c) elastohydrodynamic coupling. Moreover, in current discrete simulations, the tangential hydrodynamic lubrication force is estimated from the gap corresponding to the squeeze flow component. FMBEM allows a more realistic estimation of the gap by allowing the pressure developed in the converging flow at the inlet of a sliding hydrodynamic (HL) or elastohydrodynamic (EHL) contact to be computed. Unlike many simulation schemes, it is possible to model transitions from fluid film to solid-solid interparticle interactions and vice-versa, which often dominates the behaviour of wet particulate systems. The main limitation of FMBEM is that it is limited to linear systems and thus is only suitable for elastically deforming particles. Currently, software is being developed for massively parallel GPUs clusters for application to the modelling of twin-screw simulation. The paper will exemplify the method by considering the impact of a cluster of four close packed particles coupled by pendular liquid bridges and the results will be compared with an analytical approximation.
**42. CAPILLARY RISE INTO HETEROGENEOUS SYSTEMS**

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Wetting of solid particle surfaces is a key factor in many industrial processes and applications. Especially, in granulation processes of particles, the interactions between the binder liquid and the particle surface is decisive for the quality of the final product [1]. During disintegration of powders the wetting of solid particles by a liquid often represents the time limiting step [2]. It is obvious that the wetting behaviour has a major impact on the production as well as on the final usage of powdered materials. A wetting process becomes challenging if hydrophobic surfaces are present in a powder and water is the desired wetting liquid.

Therefore, in this study, the dynamic wetting behaviour of powder mixtures containing hydrophilic and hydrophobic surfaces with water were investigated. Untreated and silanized glass was used as model hydrophilic and hydrophobic material. Experiments were carried out in a single gap setup to identify effects on a micro scale as well as in a packed bed to determine wetting phenomena on a larger scale. Both experimental investigations show a high impact of the hydrophobic component on the wetting behaviour. As can be seen in figure 1, the wetting time significantly increases by adding just 1 wt% of the hydrophobic particles to the hydrophilic glass sample.

![Figure 1](image-url)

Figure 1. Dependency of hydrophobic fraction on normalized wetting time during water penetration in powder sample (glass spheres, mean diameter of 91μm).


As the pharmaceutical industry is moving from batch to continuous manufacturing, better understanding of the impact of twin screw granulation on tablet properties is required. While numerous studies have provided insight into the influence of process parameters in recent years, the influence of material properties and formulation design is still poorly understood. This study investigates the impact of twin screw granulation on tablets compressed from excipient blends. Systematic blends of mannitol, microcrystalline cellulose (MCC) and dicalcium phosphate anhydrous (DCPA), based on a mixture design, were granulated at three liquid levels. The compactability, compressability and tablettability of the subsequent tablets were compared to directly compressed tablets made from the original blends.

Overall, the granulation process and water levels influenced the compressability, tablettability and compactability of the formulations differently. The tablettability of formulations containing mannitol generally improved after twin screw granulation, unless MCC was present in the blend. Although liquid level was found to have an influence on tablettability of the formulations, it appears to have a negligible impact on compactability. These insights can aid in formulation design for twin screw granulation processes in order to meet the target tablet attributes.

Scanning electron microscope images of granules consisting of 1) MCC (34%) and DCPA (61 %), 2) mannitol (47%) and MCC (48%), showing differences in granule structure. Both batches contain 5% HPC.
44. REMOVAL OF TRAPPED FINE SILICA WITH SONIC ENERGY IN AGGREGATION OF MAGNETITE PARTICLES IN A MAGNETIC MEDIUM

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Magnetite ore is commonly concentrated in low-magnetic field drums to recover a magnetite concentrate low in silica (SiO₂). This magnetite concentrate is mainly used for steel production where SiO₂ is highly detrimental as rises up processing costs. In the iron direct reduction-electric furnace process, silica increases the consumption of energy, refractory, electrodes, additives and iron losses in slags. 0.1% SiO₂ in magnetite concentrate represents about one USD cost in steel production. This work presents results of the studies carried out on the removal of SiO₂ from magnetite concentrate at both plant and laboratory scale. These studies showed that silica appeared in the magnetite concentrate by three mechanisms, namely entrainment, heterocoagulation and locking to magnetite, being entrainment of fine size silica in agglomerates of magnetite particles the highest contribution. This trapped fine silica was difficult to remove by the washing water used in the magnetic concentration drum process. Using a batch magnetic unit, which simulated the concentration drum process, it is shown that sonic energy increased the efficiency of the washing water for the removal of trapped silica in the aggregates of magnetite particles. Sonic energy was applied in the magnetic zone where the magnetite particles agglomerated and migrated toward the magnetic pole. Applying the sonic energy to the magnetite magnetic concentration process a significant decrease of 0.4% in silica grade was obtained.
Twin-screw-extrusion is an emerging and focused method with several applications in the pharmaceutical field. With respect to the desired process conditions three different types of extrusion can be utilized such as Hot-Melt-, Wet- or Cold-extrusion. For all of them the residence time and the residence time distribution are crucial process parameters determining the duration of thermal and mechanical stress to the processed material [1, 2].

Several approaches to describe the residence time of extrusion processes are known and the most commonly applied models (Axial-Dispersion-, Tanks-in-Series- and Two-Compartment-model) and functions (Zusatz-function) were investigated. Therefore experimental data representing different process conditions was utilized from literature. The residence time distribution models were implemented and the least square method was used to evaluate the characteristic model parameters.

With special focus on the on and off-set zones of the residence time distributions as critical sections, the calculated results were analysed due to the differences between experimental and numerical data overall (normalized residual value $r_{\text{norm}}$, see figure 1). Also the comprehensibility of the model variables was investigated with respect to the interpretation for process optimization. In conclusion the Two-Compartment model is most capable to represent the extrusion data and improve the process comprehension. Moreover the correlations between the different model parameters have been revealed.

Figure 1. Residence time distribution (left diagram) according to the experimental data (dots) and fitted models (lines). Normalized residual values (right diagram) for the fitted models (lines, right axes) compared to the measured experimental data (dots; left axes).


Processes for agglomeration and granulation have the purpose of shaping powder solids. The goal of these processes is to improve product handling and to enhance the properties of raw materials for dosage or further processing. Depending on the material, area of application and target parameters to be defined, various methods and different techniques can be selected. Typically these granulation processes take place at temperatures well below 200 °C, which is in most cases entirely sufficient for the granulation of powders and liquids. However, in special cases an additional thermal treatment is necessary to achieve the specified quality or to activate binding mechanisms, e.g. an additional calcination or a phase transformation. This requirement applies increasingly with complex inorganic materials and conventionally is realized by subsequent costly process steps. A combination of granulation and high temperature thermal treatment in only one process step has not been available so far and limited the application of the usual techniques for granulation.

Glatt Ingenieurtechnik GmbH has developed a very flexible high temperature fluidized bed spray granulation system up to 700 °C. The process temperature can be adjusted between 50°C and 700 °C, if required gradually in different temperature steps. So a granulation and a chemical reaction may be done simultaneously or in sequence, as required.

The concepts behind the powerful technology will be presented as well as exemplary use cases. Based on a concrete example, it will show the novel processes flexibility. The influence of different process and formulation parameters on particle growth mechanisms, yield and material properties will be shown for the application of zeolithe granulation and activation.
47. NUMERICAL STUDY ON CELL DIFFUSION AND FORCE CHARACTERISTICS IN A NEEDLE TUBE BASED ON CFD-DEM

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Needle tube cell injection has been a very common and conventional treatment means for some diseases such as cataract and leukemia. However, the rate of survival of cells during the injection is not high because the cells endure many kinds of stresses when moving in the needle. So it is valuable to study the diffusion and force characteristics of cells in a needle tube during the injection. In this study, the cell-fluid flow in a needle tube was simulated based on CFD-DEM, and the diffusion and force characteristics of cells was investigated.

Figure 1. Simulated results of cell-fluid flow in a needle tube.
The tensile strength and porosity of pharmaceutical tablets are fundamental properties which influence the integrity of the tablets and importantly the disintegration time. The strength and porosity of a tablet is dependent on the manufacturing stresses the excipient materials are subjected to, and consequently can be controlled by careful manipulation of these conditions. In this research the effect of two fundamental stresses, i.e. the tableting load and roller compaction pressure, on tablet disintegration were investigated. Excipient materials were roller compacted using a range of pressures, and tablets were produced by compressing the consequent granules at varying tableting loads. For this study mannitol, a brittle and soluble material, and microcrystalline cellulose, a deformable and insoluble material, were investigated at varying binary ratios. The tablets were characterised by analysis of the compactibility and a flow cell imaging method was utilised to investigate tablet disintegration in real-time.
Mixing larger particles (carriers) with smaller (fines) to produce an adhesive, or ordered, mixture is a formulation technique used to promote powder flow and reduce the risk of segregation during handling and use. Within the dry powder inhalation (DPI) field, this formulation technique is extensively used as a means of counteracting the cohesive nature of micronized API:s required for deep lung penetration.

The aim of this work was to study the structural properties of adhesive mixtures through visual imaging and link this structure to the observed powder mechanics through the use of different techniques to measure the apparent flowability of powders. The mixtures, based of lactose, contained one carrier (Lactopress SD) with increasing amount of fine particles corresponding to different surface coverage ratios (SCR). From the structural analysis it was found that the fine particles predominantly gather in the cavities of the carrier particles at low SCR, which effectively increases the carrier particles densities and makes their surface smoother. This phenomenon was shown to increase the apparent flowability of the mixture. Adding more fines beyond a certain SCR would instead lead to a more irregular structure and a gradually reduced flowability.
A catalyst support is often used to disperse a catalyst material to enhance the contact area for reaction. This catalyst support in catalytic converters is in the form of a washcoat layer. Given the role of the washcoat layer in catalytic converters, its mechanical strength is of extreme importance as it determines the service life of catalytic converters.

In reality, washcoat layers are found to fail in both a cohesive and an adhesive mode. However, in the literature, there are currently limited publications that present a method capable of quantifying the cohesive strength of washcoat layer. One of these limited publications introduced a cohesive strength quantification technique in which a washcoat was made into a tablet and the tensile strength of the tablet measured as the cohesive strength of the washcoat layer [1]. Despite the novelty, there were still problems with the method suggested as tablet splitting occurred at low pHs due to a non-uniform drying system.

In the current paper, a more uniform drying system was suggested, which lead to the formation of intact tablets at low pHs. The cohesive strength of the washcoat layer was then successfully determined at these pHs.

The washcoat layer was prepared by drying a suspension of ceramic particles of known size followed by calcination. The pH of the suspension was adjusted and the drying conditions were also controlled. The strength results obtained were correlated with the motion of washcoat particles during drying to explain the various patterns of particle packing found at different preparation conditions.

Confined compression is an important manufacturing method in the pharmaceutical and related chemical engineering industries. Often polydisperse granulated powders are used as starting materials.

In this work, confined compression of binary granule mixtures has been studied experimentally and also simulated with the Discrete Element Method (DEM). Binary mixtures were made of granules formed from microcrystalline cellulose (Cellets provided by HARKE Pharma GmbH). Tablets were formed from the mixtures using a materials testing instrument at a maximum applied pressure of 200 MPa. Compression data was analysed using the Kawakita equation. A multi-body contact law that accounts for contact dependence resulting from contact impingement and plastic incompressibility/geometric hardening was used in the DEM simulations [1]. Two different size ratios (10 : 1 and 3.5 : 1) were investigated experimentally whereas simulations were performed for a size ratio of 2 : 1.

From the experiments it was found that both the Kawakita $a$ parameter (the maximal degree of compression) and the $1/b$ parameter (that indicates the pressure required to reach a degree of compression of $a/2$) exhibited parabolic dependencies on composition (fraction of large particles). The smallest values of the Kawakita $a$ parameter and the largest values of the $1/b$ parameter were obtained at an intermediate composition. This behaviour was captured by the simulations.

The measured tensile strength of the formed tablets generally decreased with increasing fraction of large particles. However, for the large size ratio, percolation-type behaviour was observed, such that the tensile strength levelled out once the fraction of large particles exceeded a threshold value.

Example of particle arrangement during compression of a binary granule mixture as obtained from DEM simulations.

Multi-stage fluidized beds are frequently used for particle layering in industry. One advantage of such fluidized beds is that they can achieve a high throughput by being operated continuously. Horizontal fluidized bed is the most common used multi-stage fluidized bed in industry. Normally, the size distribution of particle (Fig. 1(a)) has become an issue of the feed material. On the other hand, unlike granulation in batch fluidized bed, the particle residence time distribution (Fig. 1(b)) has a great influence on the granular product. Thus, it is worthwhile to add these two factors to the modelling of granulation in such fluidized bed.

In this work, γ-Al₂O₃ particles were granulated in a pilot scale horizontal fluidized bed. For each experiment, the particle size distribution and the residence time distribution were measured and analysed. To account for the particle back-mixing effect when describing the experiments, a fluidized bed granulation was expanded by a one-dimensional population balance that considers the particle residence time distribution. Experimental particle residence time distributions were reproduced by means of the tank-in-series model. Subsequently, the particle size distribution was implemented as a second dimension of the population balance to the model. Figure 1(c) shows the preliminary simulation result of the product mass flow rate under the two previously mentioned dimensions.
INFLUENCE OF PARTICLE SIZE AND SHAPE OF PARAFFIN POWDER ON THEIR COMPRESSION BEHAVIOR AND COMPACTION PROPERTIES

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Paraffin is a material used in many industrial fields: waxing paper, candle making, food coating, pharmaceutical and cosmetic industries... Paraffin wax is often used in powder form in order to produce solid material by direct compression. Understanding behaviour of powder during compression is then of major interest. Thus, investigate the influence of particle size and shape on powder compression and compaction provides a way of choosing the type of powder to promote when working with paraffin according to the application performed.

To this day, many studies deal with compressibility and compatibility of powders but the behavior of paraffin is poorly documented. This study highlights the influence of particles size and shape of paraffin powders on their compressibility and compaction properties. It should be noted that the size of particles studied here is relatively large (1 to 2.5 mm). In order to highlight different behaviours induced by particle size and shape, 7 powders with different characteristics were studied. These were obtained by spraying of hot paraffin.

Particle size and shape were measured by digital image analysis, using images obtained with a scanner. This approach allows a fast and accurate study of the particle size since a large number of particles is taken into account in each image. It also quantifies the particle shape. Compression was measured by compressing powder in a mould, using a texture analyser (JJ.Lloyd® LR5K). Secondly, the pellets formed therefore undergone a stress test in order to evaluate their compactibility. Pressure is applied at a constant rate until failure of the pellet. The corresponding pressure is defined as the strength of the pellet.

Results of compression show a good correlation with Walker model for low pressure (<0.2 MPa) and Heckel equation for higher pressures. These pressure ranges can be correlated to the different stages of compression: the first corresponding to the rearrangement of particles and the second to plastic deformations.

Comparison of the different powder types shows that the low-pressure compression is governed by the average circularity. The more particles are spherical, the more they are difficult to compress at low pressures. This is related to primary arrangement (initial density) that is more compact for circular powders. The compression at a higher pressure appears to be governed by the uniformity of size. The most homogeneous powders are, the more difficult is the compression at high pressures. This study also provides a way to compare the apparent plasticity (P₃) of paraffin.

Finally, the strength of pellets is studied. It is evidenced that strength is far greater when pressure applied during compression is high. Similarly, for a given powder, the higher the density is, the greater its strength will be. Tablets strength is related to its behaviour during compression and thus, also to the size and shape of particles.
In the roller compaction process, powder flow properties have significant influence on the uniformity of the ribbon properties. The objective of this work was to improve the powder flow in the feeding zone by developing novel feeding guiders which were located in the feeding zone close to the rollers in the roller compactor. Three different designs of novel feeding guiders were applied to control the amount of powder passing across the roller width. The novel feeding guiders were used to guide more powder at the sides between the rollers and less powder at the centre comparing to the original feeding elements. Temperature profile and porosity across the ribbon width indicated the uniformity of the ribbon properties. Using the novel feeding guiders resulted in producing ribbons with uniform temperature profile and porosity distribution across the ribbon width. The designs of the feeding guiders contributed to the improvement of the tensile strength of the ribbons produced from the compaction stage and the reduction of fines produced from the crushing stage.
The formation of hetero-aggregates from oppositely charged hydrogel microparticles was investigated. The primary particles—negatively charged alginate and positively charged chitosan microgels with a mean diameter of 6-7 µm—were produced by spray drying with in-situ cross-linking [1]. The kinetics of their hetero-aggregation in the aqueous environment was measured on-line by static light scattering. The effects of the starting stoichiometry (alginate:chitosan particle ratio), hydrodynamic conditions (agitation intensity), and pre-conditioning (dry vs. partially hydrated particles) on the aggregates' growth kinetics and the asymptotic size distribution were systematically investigated. An optimum stoichiometric ratio of the primary particles was found in each case. The structure of the resulting hetero-aggregates was characterised by laser scanning confocal microscopy and found to strongly depend on the pre-conditioning of the primary particles. While dry primary particles resulted in open, flocular structures, pre-hydrated primary particles gave rise to relatively dense, compact aggregates [2]. The hetero-aggregation process was shown to provide a platform for the formation of well-defined structures that can be further used in applications such as the encapsulation and release of multiple actives from a single carrier.

Figure 1. Scheme of hetero-aggregation (a) and laser scanning confocal microscopy image of aggregates composed of chitosan (yellow) and alginate (red) particles at mass ratio 1:1 (b).


**56. PREDICTION OF SELF-HEATING IN SPRAY DRYER WALL BUILD-UP**

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In the spray drying of detergent powders, it is common for layers of powder to accumulate on the inner walls of the spray drying tower. At the high operating temperatures of the spray drying tower, the detergent powders in question are known to undergo the process of self-heating, whereby exothermic reactions occurring in the powder layer can cause the core temperatures of these layers to increase significantly. If sufficient self-heating occurs then the powder begins to char, with these charred particles compromising the quality of the final product, while in extreme cases thermal runaway can occur. Being able to predict this behaviour through the characterisation of these powders and modelling of these systems will not only help to limit these problems, but will allow the optimisation of the process for current and new detergent powder formulations.

Characterising the detergent powder involves measuring the self-heating reactions kinetics and other heat transfer properties that influence this behaviour. Different methods such as the cross-point temperature method, steady-state basket method, and thermogravimetric analysis have been applied to explore different reaction models for the powder. This work compares these methods and aims to establish the best means of determining these kinetics and the reaction model most representative of the observed behaviour.

By applying the measured reaction kinetics and heat transfer properties, and by building on existing models of similar systems, this work aims to model the self-heating behaviour of baskets of detergent powder using a 2D transient coupled conduction and reaction model. Having validated the model against temperature profiles measured during the baskets experiments, it has been successfully used to predict the critical external temperature of a number of different sized baskets of detergent powder. This model can then be adapted to predict the self-heating behaviour in spray drying tower wall build-up, and explore the effects of build-up properties and tower temperature on this behaviour. This model will also allow optimum tower temperatures and process conditions for current and new detergent powder formulations to be determined.

Illustration of the detrimental effects of self-heating on detergent powder quality.
57. ENERGY EFFICIENCY AND SCALE-UP OF FLIDIZED BED COATING PROCESSES WITH TEMPORAL SEPARATION OF LAYERING AND PARTICLE DRYING

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Due to the progressive increase of prices for energy and its production an optimization of technical processes with regard to energy consumption becomes more and more an important issue. Energy demanding production processes, such as fluidized bed layering granulation and coating provide an enormous potential for energy savings. The reduction of the specific energy consumption can be achieved by heat recovery from the exhaust air or process intensification, e.g. via separation of subprocesses of the granulation process.

The present paper examines the temporal separation of process steps like growth and liquid evaporation as one way of intensification of batch processing. In order to optimize both subprocesses, granulation and particle drying, are operated alternating by switching the spraying rate and other process parameters.

Temporal separation also offers the opportunity to operate the drying phase under packed bed conditions instead of energy demanding fluidized bed condition. Also the process can be divided in several periods of granulation and drying, which is subsequently called intermittent operation. Experiments have been carried out to investigate the influence of the way of drying and the number of periods on energy consumption and product quality (particle size, particle moisture content, shell porosity) on laboratory scale as well as pilot scale. Additionally model calculations have been performed for the purpose of validation. The results have been used to calculate the specific energy consumption of the different investigated process variations in order to estimate their economic feasibility and to draw a comparison to the conventional process. Plant size is taken into account.

The outcome shows that a process design with the shortest duration performs best with regard to operation costs and overall economic feasibility.
In the pharmaceutical industry, dry granulation by roll compaction is a process of size enlargement used to produce granules with a good flowability for further die compaction process. However, how granulated formulations behave during die compaction and why they exhibit behaviors different from those showed by the blended formulations is still a challenge. The aim of this work is to explore the differences of the compaction behaviors of raw and granulated material of MCC 101 under stressing, based on the analysis of the main parameters of particulate solids, proposed by Drucker-Prager Cap (DPC) model, which is commonly used in the field.

To go further in the investigation, ribbons of relative density 0.57 were produced by roll-compaction and milled using an oscillating mill. Then, granules were sieved into two size classes to study the effect of granule size on the compaction behaviour. Using the standard procedure of DPC calibration (full instrumented die compaction press, diametrical strength and unconfined uniaxial strength), the material parameters for raw material and both granules size classes were determined in the range of relative density 0.4 – 0.9.

It was found that all the studied parameters differ from raw material to granules, mainly at low levels of densification. In addition, the increase of the granule size had an effect on the DPC parameters. This leaded to the attainment of different yield surfaces curves for the different materials. The yield surface was expanded for the raw material and it was contracted when the granule size increased.

In contrast to our results, Mitra et al. [1] found that the yield cap curves for all the materials (raw and granules) were overlapping for the same tablet density. The only observed impacted parameter was the cohesion. Nevertheless, they used cylindrical mono-disperse granules with high density and the results may be different to the ones of roll-compactied granules.

Theobromine (TB) is a xanthine derivative with bronchodilator, vasodilator, and smooth muscle relaxant effects [1]. High doses of TB required for oral administration due to its low solubility leads to significant adverse effects. This work aimed to increase the dissolution profile of TB using Hot-Melt Extrusion (HME). Three hydrophilic polymers were selected, namely Soluplus® (Solo), Plasdone™ (Plasd) and Eudragit® E PO (EudE) and were processed in a Haake Mini CTW (Thermo Scientific®) in a proportion of 7:3 (w/w) with the drug. Dissolution profile, as well as optical microscopy, differential scanning calorimetry (DSC) and X-ray powder diffraction (XRPD) assays were used to evaluated TB as supplied and the HME granules. HME granules showed a uniform appearance by optical microscopy which could not be distinguished from the original aspect of crystalline TB and polymers. All extrudates exhibited faster drug dissolution compared to the non-extruded drug, especially the granules containing Plasd and EudE (Fig. 1A). Moreover, whereas less than 80% of the drug as supplied dissolved after 3h, more than 85% of TB from HME granules was dissolved at the same period. DSC analyses of TB (Fig. 1B) exhibited a crystalline profile with melting at 249.3 °C. HME granules showed a broad endothermic peak related to the decomposition of the polymers, together with the drug melting in a range of 250-345 °C. XRPD (Fig. 1C) confirmed the TB crystalline profile. The same crystalline state of TB was detected in all HME granules; however, there were a strong amorphous component in such material indicating a partial drug amorphisation, which could explain the fast dissolution of TB from HME granules. Our findings together demonstrated the feasibility of using HME to increase TB dissolution, with good perspectives to enhance the bioavailability of this drug.
Targeted release and stability of active ingredients within a product formulation is one of many challenges faced in the cost and performance driven consumer goods industry. Revolymer’s solid particle processing technologies aim to provide long-term shelf-life of actives within detergents whilst at the same time achieving fast, complete release of the ingredient at the point of use. Incorporation of solid particles into a formulation requires free-flowing, dust free particles of defined size, shape and density; particle processing is therefore an important factor to consider when designing active granules for use in detergents.

A study of the stabilisation and performance optimisation of antifoams within powder laundry detergents is presented. Various processing methods have been employed to produce granules containing the active antifoam in combination with Revolymer proprietary polymer ingredients within a stabilising matrix. Processing methods included granulation, extrusion and spheroidisation with subsequent physical characterisation of resulting pellets. Antifoam efficacy was monitored using foam collapsing experiments and resulted in the development of free-flowing, rapid release particles.
Bioavailability and solubility of poorly soluble drugs is potentiated when the cohesive forces between solute and solvent becomes greater than that of adhesive forces. Moreover, by incorporating superdisintegrants i.e. crosscaramellolose sodium, Kyron-T134 and sodium starch glycolate etc. and surfactants like sodium lauryl sulphate promote rapid disintegration and transfer across natural barriers of gut.

In this work, successful efforts have been exercised to overcome bioavailability issues of a hydrophobic drug. Powder blend containing inclusion complexes was thoughrely mixed to attain uniform distribution and analyzed for micromeritic properties i.e. bulk and tapped density, hausner's ratio, carr's index. Drug polymer interaction was confirmed by FTIR studies. Stability of drug in developed MDT's was assessed by DSC and TGA studies. Crystalline or amorphous nature was confirmed by PXRD studies. MDT's were compressed using direct compression technique. Post compression studies were performed e.g. friability, disintegration, dissolution, hardness, thickness, diameter, wetting volume, water absorption ratio, weight variation, solubility studies etc. A potential approach for bioavailability enhancement was successfully developed.
Powders often exhibit poor flow and granulation can be applied to improve these powder properties. Wet-granulation is an important process in pharmaceutical manufacturing since drugs and excipients tend to have poor flow and compaction properties. An important aspect of controlling this process is the understanding of solid-solid as well as solid-liquid interactions. Poor drug-binder adhesion often leads to insufficient binder spreading and undesired granule and tablet properties. Surface energy measurements of the individual formulation components may be used to predict drug-binder interactions.

The surface energy is directly related to the work of adhesion and the ratio of adhesion to cohesion would provide information on the compatibility of drug and excipients [1]. Both properties depend on the energetic situation on the surface of the materials which is commonly expressed by the surface energy. Surface energies are traditionally measured by wettability or contact angle methods. However, there are many disadvantages with this technique including the poor reproducibility as well as the limited sensitivity when used on powders. Therefore, the contact angle method has had limited success in wet-granulation studies [2]. However, Inverse Gas Chromatography (IGC) and Dynamic Vapour Sorption (DVS) have become a popular alternative due to the ease of application and high sensitivity and reproducibility.

The drugs Acetaminophen and Ibuprofen have been studied as well as the binders HPC, HPMC and PVP. HPC showed the strongest adhesion, followed by HPMC and PVP. This correlated well with the trends in tablet hardness and friability. The higher the work of adhesion the higher the tablet strength and the lower the friability.


Identification of powder and granule Critical Quality Attributes to assist in pharmaceutical product
development and manufacturing control is under consideration in both Europe and the USA. To
measure the properties of materials intended for tablet compression requires a suitable instrument. In
the past this has only been possible using an instrumented tablet press or a compaction simulator. We
have developed a benchtop powder compaction analyzer\(^1\) which fully characterises a material quickly
and easily to measures punch force and punch position during powder compaction, detachment, and
ejection. These can be interpreted to characterise the manufacturability of the granule before it is put
into Production.

The properties of approximately 50 materials have been measured including granules and
pharmaceutical excipients in common use. Testing of additional materials is continuing. These data
have been used to set parameter ranges for granule Critical Quality Attributes and have been ranked
on a five point ranking scale. This scale enables the user to easily see which granule properties are
acceptable for compaction and lubrication, and which require further improvement.

Compaction data at a range of forces, and user measurements of tablet thickness, weight and
diametral breaking load, are collated in a single spreadsheet which automatically generates the
parameters listed in Table 1. The elements of a typical summary report for wet granulated
paracetamol are listed in Table 2. The parameters are derived as follows. The CQA values for
tabletability relates to the ability of the tablet to withstand packaging and transport. Poor
compactibility is related to capping risk from over-compression and poor water penetration. Ejection
and detachment stresses are linked to lubrication issues; tablet defects such as picking and sticking
are strongly related to ejection stresses above 5 MPa. Evaluation of the properties of a single tablet
formulation, prepared using three different granulation methods resulted in clear differences in
manufacturability as assessed by the protocol and indicated which formulation would be most suitable
for manufacture.

\(^1\) Gamlen Tableting Ltd, Nottingham
Spray fluidized bed agglomeration is used to produce raspberry-like particle aggregates from powders. This technique is mainly used in food, pharmaceutical and chemical industries. With spray fluidized bed agglomeration, e.g., flow properties of powders can be improved, dustiness can be reduced, bulk density can be modified or instant properties of powders can be enhanced. Especially in food industry instant properties of powders need to be improved, e.g. for powdered soup. Thus, maltodextrin DE 12 is used as a model substance for the presented experiments.

To realize high product throughput, the process of spray fluidized bed agglomeration can be performed in continuous operation mode (Fig. 1, left), to which scarcely any literature can be found. Therefore an initial amount of maltodextrin (d50 = 170 µm) is filled into the fluidized bed and sprayed onto with water. The partly amorphous powder particles undergo glass transition and become sticky at the particle surface, thus, allowing for agglomeration of the powder. Product is withdrawn continuously from the fluidized bed by a classifying tube installed centrally in the distributor plate. Fresh powder (nuclei) is supplied externally and fed into the fluidized bed continuously as well. For this process configuration, the volume flow rate and, thus, the velocity, of classifying air and the nuclei mass flow rate were varied. High classifying velocities and low nuclei mass flow rates resulted in large particle sizes in the fluidized bed and in the product. After 1.5 to 2 h the experiments reached stationary steady state (Fig. 1, right).

Figure 1. Plant scheme for continuous spray fluidized bed agglomeration (left); particle size distribution density q3 for the reference experiment (right).
The aim of this study was to evaluate the twin-screw granulation process for both hydrophilic and hydrophobic formulations to understand the role of the individual screw modules and process settings, as well as their interaction upon granule formation. This involved investigating the influence of process settings on granule properties at different locations in the granulator barrel. Results from this experimental study will be used for the development, calibration and validation of a two-dimensional Population Balance Model (PBM) describing particle property changes (granule size and liquid content or density/porosity) during twin screw granulation.

One hydrophilic and two hydrophobic formulations were granulated using the high shear wet granulation module of the ConsiGmaTM-25 system (GEA Pharma systems, Collette, Wommelgem, Belgium). To develop and calibrate the 2D PBM model, a 3-level full factorial Design of Experiments (DoE) was performed for three formulations by varying the following parameters: screw speed (450-900 rpm), material throughput (5-25 kg/h) and liquid-to-solid ratio (formulation dependent). The temperature of the cooling water around the granulator barrel was kept constant at 25°C. This DoE was executed for one screw arrangement existing of 2 kneading zones of each six kneading elements ordered at a stagger angle of 60°. Several responses like moisture content, particle size and density/porosity were assessed along the length of the barrel.

This experimental study proved the ability to capture the stepwise formation and transition of granules at the different locations inside the granulator in terms of granule properties (e.g. granule size, moisture, porosity, etc.). It was affirmed that process parameters like liquid-to-solid ratio can dictate the formation of granules and their corresponding quality attributes.
Dynamic Vapour Sorption (DVS) has been widely used for investigating the interaction of water vapour with active food and pharmaceutical ingredients, excipients and formulations. The moisture sorption properties of these materials are recognized as critical factors in determining their storage, stability, processing and application performance [1]. A few applications of DVS include hygroscopicity, moisture content, moisture-induced phase transitions, hydrate formation/loss, and amorphous content.

DVS is a well-established method for the determination of vapour sorption isotherms. It is based on a highly sensitive gravimetric system, which measures the adsorption and desorption of extremely small amounts of probe molecule. The ability to use organic vapours besides water allows the DVS instrument to be used for some unique applications. The instrument also has the ability to couple in-situ video microscopy and spectroscopy (Raman and/or Near-IR) with the gravimetric sorption measurements which allows for the investigation of vapour-induced morphological and structural changes in the material. The presentation will describe the operation of the DVS and show some applications to illustrate how the DVS technology could be applied to a wide range of food and pharmaceutical materials [2, 3].


67. TWIN SCREW GRANULATION OF HYDROPHOBIC/HYDROPHILIC POWDERS: THE EFFECT OF KNEADING ELEMENTS AND SCREW SPEED ON THE EXTENT OF GRANULE FORMATION

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Fundamental challenges in wet granulation have been to conquer the preferential wetting problems which are notable when using hydrophobic formulations due to the powders’ poor wetting properties. These problems have a significant effect on the final granular product. This is particularly important with twin screw granulation where it is necessary to have a full understanding of the process to improve the granule size and strength. The current study investigated the extent of granule formation in twin screw granulation using a mixture of hydrophilic/hydrophobic powders. The process parameters examined were the length of the kneading section and the screw speed using water as a granulation liquid. To characterize the granule properties, the extent of granule formation, granule strength and shape were studied. A longer kneading element mixing length was found to significantly improve the mixing of hydrophilic/hydrophobic powders thereby increasing the extent of granule formation. However, the granule strength was found to have a stronger dependency (decrease) with increase in screw speed. The transitions in the granule shape observed with a longer kneading element mixing length are attributed to the changes in granulation mechanisms.
68. USAGE OF SPOUTED BED TECHNOLOGY TO COAT AEROGEL PARTICLES

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Due to their high inner surface area and open pore structure aerogels are used as matrices for active compounds in food products. To protect the particles and active ingredients from environmental impact during storage and to design a controlled drug release, a protective layer is needed [1].

In this work the functionalization by coating of micrometer-sized (<100 µm) and light-weighting protein-based aerogels is performed in a novel prismatic spouted bed apparatus. To achieve stable process conditions these fine particles are highly dispersed in the apparatus at high gas velocities (so-called dilute spouting regime). This procedure is excellent for coating of fine particles with dense, thin and uniform layers (Fig. 1 left) enabling the production of sustainable particles, which provide new options for food and pharmaceutical applications. The influence of different process parameters, like nozzle air flow or droplet size on the coating layer is investigated. For this purpose particle growth and coating layer quality are measured. The layer thickness of coated particles is determined e.g. by cross-sectioning using FIB instrument (Fig. 1 right). A huge decrease of specific surface area of treated particles indicates a uniform coating on their surface. Additionally a coupled CFD (Computational Fluid Dynamics)-DEM (Discrete Element Method) simulations are performed to optimize the coating process.

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Figure 1. Left: SEM of spouted bed coated protein-based aerogels, right: SEM of FIB cross-sectioning of a coated particle in order to measure the layer thickness.

Wet granulation of fine powder is a widely used technique in many various industrial sectors for engineering intermediate and final products such as food, detergent and pharmaceutical [1, 2]. The physical and mechanical properties of granules are affected by the internal structure which in turn is influenced by both formulation as well as process conditions. Controlling the granulation process enable improvement of the granule behaviour such as flow, strength handling and performance [3]. In this paper, a study on granules produced using different two scale granulators (0.5 and 2 L) and the effect of different process conditions such as impeller speed and volume of materials on the properties of granules are reported. Calcium carbonate powder was used as the primary particles. A 65 wt.% aqueous solution of polyethylene glycol 4000 was used as the binding agent. The liquid/solid ratio was 10 wt.% [3]. The Mi pro High Shear mixer Granulator manufactured by ProCepT with two set-up capacities of 0.5 and 1.9 L was used for granulation. Three different volumes of material (0.125, 0.250 and 0.375L for 0.5L) and (0.50, 1.0, 1.5L for 1.9L) were conducted. For each volume at each scale different impeller tip speeds (3.5, 4.13, 5.39 and 6.12 m/s) under various process times were applied.

The effect of both scales with various impeller tip speeds and different volumes of material on the granules strength and size have been quantified and is reported in this paper.


**A PROPOSAL FOR A DRUG PRODUCT MANUFACTURING CLASSIFICATION SYSTEM (MCS) FOR ORAL SOLID DOSAGE FORMS**

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The first Manufacturing Classification System (MCS) paper [1] was written not only to summarise the current state of knowledge around the factors determining process choice for oral solid dosage forms but also to put a call-out to the wider pharmaceutical science community for feedback. As part of this process, the MCS team conducted conference roundtables, quarterly teleconferences and an online survey to find out what API properties were important when selecting or modifying materials to enable an efficient and robust pharmaceutical manufacturing process. The most commonly identified factors were:

1. API particle size: Small particle sizes are known to increase risk of processing issues e.g. electrostatics, flow, sticking.

2. Drug loading in the formulation: High drug loadings allow formulators less opportunity to mitigate poor API properties through the use of excipients designed for oral solid dosage forms.

The next step was to establish linkages between these parameters and process decisions in the real world. This data though is generally proprietary and / or difficult to access in the public domain. To overcome this, the team identified publicly-available proxies for these important parameters: Bio-Pharmaceutics Classification (BCS) class (in place of particle size) and dose (in place of drug loading). Poorly soluble BCS Class 2/4 were seen as more likely to have controlled (smaller) particle size than highly soluble BCS Class 1/3. Analysis of 370 tablet formulation applications in European Public Assessment Reports (EPAR) revealed that, as dose increased, there was a shift from direct compression to roller compaction to wet granulation. This shift happened at lower doses for BCS Class 2/4 compounds compared to BCS Class 1/3. In summary, this showed that higher doses and more poorly-soluble API increase the likelihood of having to opt for more complex processing routes.

The assumption for particle size was tested by accessing a dataset relating to historical commercial tablet products (n=15). This showed that for dry processes, there was a link between particle size and achievable drug loading as determined by percolation rate i.e. smaller particle size led to lower achievable drug loading. The link was less clear for wet granulation processes as other formulation components may dissolve leading to surface effects.

Solid urea is the largest nitrogen fertilizer product which is produced in two forms of granules and prills. Although the chemical properties of both prills and granules remain similar, their different physical and mechanical properties are distinguishable and make them suitable for different application either as fertilizer or raw materials for chemical industry. The main objective of this work is to compare and characterize the physical and thermal properties of urea prills and granules and analyses the finishing processes of urea for each sample obtained from different sources. The characterization were conducted using TGA, DSC, KF titration, Scanning Electron Microscopy (SEM), HPLC and sieve analysis.

Karl Fischer titration determined the moisture content in granules to be 0.48% compared to the prills being 0.34%. The moisture content of a fertilizer during storage and handling affects the physical quality. HPLC analysis on biuret content showed the prilled samples to have a higher biuret content. Results of the sieve analysis technique to determine the size distribution show granules having a larger mean diameter of 2.81 mm compared to prills with a mean diameter of 1.64 mm. Analysis of the structure of the urea samples using SEM technique displayed the prills appeared more smooth and glassy. Looking at the inner structure, the granules showed the inner layer to be more solid and dense, in contrast to the prills which were shown to have fractures along the entire surface.
SEEDING GRANULATION OF DETERGENT POWDERS

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Granulation process transforms fine powders into free-flowing, dust-free granules with the presence of liquid binder at certain operating conditions. The main focus of this research is on seeded granulation of detergent powders, a new phenomenon of granulation in which a layer of fine powders surrounds the coarse particle. This is already proven for calcium carbonate in the previous study (Rahmanian et al., 2011). Here, detergent granules were produced in a 5 L high shear Cyclomix granulator using different fine/coarse powder ratio (1/3, 1, 3) and different binder ratio of 10% of 20% and different binder addition method of once and gradually. The granules were then characterized for their particle size distribution, strength and structure. It was found that a high percentage (86.86 wt. %) of granules in the desired size range between 125-1000μm were produced using the powder ratio of 1/3 with binder content of 10%. Highest mean crushing strength (2.12N) with a narrow distribution was obtained using this condition and no seed was found at the powder ratio of 1/3. Structure characterization of the detergent granules produced in Cyclomix granulator shows that consistent seeded granule structures are produced under the optimum process and formulation conditions of 1/3 powder ratio regardless the amount of liquid binder and the binder addition method.

Seeded granulation is introduced as a new method of granulation in which all produced granules in desired size range have a large particle at their core surrounded by finer particles. Such granules have previously been reported where calcium carbonate (Durcal 65) was granulated with aqueous polyethylene glycol (PEG) as the binder [1]. The aim of this study is to fully characterize and compare the physical and mechanical properties of two different types granules produced in Cyclomix high shear granulator, i.e. seeded and classical (non-seeded) granules. The materials and formulation are kept identical and only impeller speed was changed to produce the classical granules. The granules produced were dried and sieved into various sizes. Characterization was later carried out on the granules to analyze their shape, strength, size, flowablity and internal structure. It is observed that seeded granules are more spherical and their flowablity, measured by Schulze shear cell, is significantly improved as compared to classical granules. Seeded granules also showed less porosity and higher strength as compared to the normal granules.

Large (x50,3: 1200 µm [1]) and small inert pellets (300 µm [2]) were coated with a model drug by fluidized bed coating and in a second step by a functional polymer for controlled drug release. Particle size was measured in-line over the whole processes by a spatial filter velocimetry (SFV) probe. Particle size as well as coating layer increase and undesirable agglomeration were detected what gives the possibility of coating process control and intervention in risk situations.

The aim of the project was the comparison of in-line (SFV probe) with off-line particle size data from photo-optical method (Camsizer®) and sieve analysis in the fluidized bed coating process of small pellets with model drug sodium benzoate. The theoretical thickness of the layer was calculated from the true densities of the formulation components.

Therefore, Cellets®200 were coated with increasing amounts of model drug (ratio core:coating 1:0.1 to 1:0.5). The coating processes were stable but with increasing process time distinct material losses by abrasion and spray drying could not complete prevented. Nevertheless the yield of coated pellets amounts above 90%, decreasing with increasing process time. With increasing coating layer sphericity increases giving hints to stable processes. The quotient of the medians of number and volume density distribution is constant indicating the absence of remarkable agglomeration. Layer thickness values of the SFV probe meet the calculated values. Camsizer values are insignificant above the values of the probe (in both methods the chord length is used for data evaluation) and the calculation. The similarity of calculated and measured layer thickness points to compact layer formation without hollow space. Sieve analysis values increase with layer growth but are much higher due to gravimetric evaluation.

In a second trial, pellets were coated with sodium benzoate in a ratio core to coating of 1:1. At several time intervals samples were withdrawn from the process for off-line particle size investigation. The medians of volume density distribution increase nearly linear with process time and corresponding layer growth (coefficient of determination above 0.98) for both SFV probe and Camsizer. The latter are once more slightly increased compared to SFV probe values. Off-line Camsizer measurement and calculation on the base of true density are suitable for the verification of in-line SFV probe data.


DEVELOPMENT AND OPTIMIZATION OF MINITABLET FORMULATION EMPLOYING ACETAMINOPHEN AS MODEL COMPOUND AND HIESTAND QUALITY BY DESIGN METHODOLOGY

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Interest in minitablets used as multiparticulate oral dosage forms is currently increasing, especially for pediatric application. Minitablet production requires exact control of process parameters and excellent powder flow to ensure weight uniformity despite small dies.

The aim of this work is designing a minitablet formulation using the model compound acetaminophen and employing quality by design principles. Among them, the characterization of mechanical properties of pure substances according to the Hiestand approach [1] was implemented in order to improve the rationale selection of different excipients. Additionally, for powder blends, the prediction model developed by Amidon [2] was employed with the aim to evaluate in advance the resulting mechanical behaviour of a defined formulation and drug load. Experimental confirmatory tests of selected simulated powder mixtures were also conducted.

Four formulations using different qualities of microcrystalline cellulose (MCC), namely Avicel PH101 (A), Avicel HFE102 (B), Avicel PH102 (C) and a 3:7 mixture of Avicel PH101 and Isomalt (gelenIQ721) (D) were analysed with regard to flowability by different methodologies, e.g. ring shear cell and bulk/tapped density. Minitablets were manufactured by direct compression employing a rotary press and multitip tooling. After compression the minitablets were characterized with regard to weight uniformity, height and tensile strength.

As a main result a maximum of 30% drug load in combination with MCC as main filler showed to be feasible with regard to tabletability of acetaminophen. Additionally, influence of flowability on weight uniformity of the resulting mini tablets could be shown as well as influence of excipient selection on compressibility and resulting mechanical properties of tablets. Confirmatory test of powder mixtures exhibited good accordance with predictions.


In the sintering process, granulation is typically carried out in continuous drum granulators using water as a binder. It involves multiple components besides iron ores, such as fluxes (limestone, lime, olivine or dolomite), solid fuel, return fines and other recycled materials. The granulation process is influenced by the characteristics of the input materials and by the action of cohesive forces enhanced by the drum granulator. The main variables affecting the motion of particles in a drum are the rotational speed, filling degree and particles size distribution and shape. As it is necessary to maintain a consistent quality of the granules (size distribution, porosity, strength, etc.) despite of the varying iron ore properties, the following question arises: how does the quality of water influence the granulation process and the granules strength?

The objective of this work is to study the effect of water quality on the kinetics of iron ore granulation and to identify the factors which influence granules strength. The raw materials used in the granulation experiments are three commercial iron ores (identified as goethite, hematite and magnetite) and return fines. Those materials have been deeply characterised. Mineralogical analysis of iron ores and return fines have been achieved using multispectral imaging coupled with an image processing in order to well distinguish the iron minerals. Specific surface area has been measured by adsorption of nitrogen at low temperature and application of the adsorption isotherm equation of Brunauer, Emmett and Teller (BET). Porosity has been obtained by mercury porosimetry.

The influence of different kinds of water on the kinetics of the granulation process has been investigated with an ideal system only composed of nuclei and fine particles of the same iron ore. The studied parameters are the PH, temperature and electrical conductivity of the water. For ore-ore mixes, the outputs were the granules median size (D50), the granules strength and the permeability. It can be seen that, for the three ores, the granule strength increases when the electrical conductivity increases. The colloidal matter plays also a role, we find a relation between the zeta potential of iron ores and the strength of granules.

Figure 1. Drum granulator device and granule strength measurements.
The ribbon porosity is a critical quality attribute in roll compaction/dry granulation (RCDG), as it predominately determines the granule porosity and granule size distribution. Considering the increasing importance of RCDG, a reliable method to monitor the ribbon porosity in-line is desired. So far NIR spectroscopy and NIR chemical imaging have been used in experimental set-ups [1]. Both techniques require expensive equipment and complex data processing. A new and so far unpublished approach is to derive the ribbons relative density (= 1 - porosity) from the ribbon temperature, measured by a thermographic camera.

The aim of this this study was to investigate the applicability of this method to materials with different a deformation behaviour. For this purpose a plastically deforming material (microcrystalline cellulose (MCC), Vivapur 102, JRS) and a brittle one (dibasic calcium phosphate anhydrous (DCPA), Budenheim KG) were chosen. Both were roll compacted on a Gerteis Minipactor at five different specific compaction forces (SCF). All experiments were conducted once with cheek plates and once with rim rolls. The freshly formed ribbon was recorded with a thermographic camera (optris PI 640, optris GmbH), collected and the porosity determined using powder pycnometry (GeoPyc, micromeritics) as a reference method.

Figure 1 displays the average ribbon temperature at various SCF's. It shows that the temperature increased with higher SCF's for both materials and for both sealing systems. The slope is in the same range for all curves, while the y-intercept varies. MCC led to higher temperatures than DCPA and cheek plates to higher temperatures than rim rolls. Figure 2 displays the same temperatures plotted against the relative density of the ribbons. It reveals a strict correlation for all set-ups and materials and a strongly material depended slope.

The data presented in this work demonstrated that a thermographic camera can be used to determine the ribbon density in-line for materials of different characteristics. It underlines the potential suitability of this technique to be a much needed PAT tool for RCDG, especially as it is inexpensive and does not require extensive data processing.

SWEETENERS ARE SOLUBLE AND STICKY EXCIPIENTS AND THEIR MANIPULATION IN HIGH SHEAR GRANULATORS MAY BE VERY DIFFICULT BECAUSE THEY CAN ADHERE TO THE MIXER WALLS OR LEAD TO AN UNCONTROLLED GRANULE GROWTH.

The aim of this research was to evaluate the agglomeration mechanism of mixtures containing cellulose microcrystalline (MCC) as bulking agent and different amount, ranging from 0 to 100% (w/w) of four different sweeteners (mannitol, sorbitol, xylitol and sucrose).

Particle size and surface area of the sweeteners were evaluated by laser light scatter and BET analysis and their solid state was investigated by XRPD.

Sweeteners of 63-400 µm size range were mixed with MCC and analysed by a mixer torque rheometer (MTR3, Caleva™) using multiple addition method in order to evaluate the different capillary state and predict the water amount necessary for the granulation experiments.

In order to characterize the wet masses behavior and highlight the dependence of torque value on amount of water, mixing time, shaft speed and liquid binder flow rate a DoE technique was used and 3D graphs were drawn. Granulation experiments were also performed in order to correlate the information obtained using the MTR3 with granule final properties.

3D graphs for the mixture containing 75% (w/w) of sucrose and 25% (w/w) of MCC.
Mini-tablets are tablets with diameter below 3 mm and are becoming increasingly more popular oral dosage form, especially for pediatric and geriatric population [1]. Tablets are traditionally coated in drum coaters however mini-tablets can be also coated using fluidized bed coaters.

In this study placebo mini-tablets with three different diameters (2.0, 2.5 and 3.0 mm) were coated using classical and swirl Wurster chamber (Glatt GPCG-1 and Brinox CGD). The effect of fluidizing air flow was investigated at two different air flow rates (130 and 156 m/h³). As a main coating result inter-tablet coating variability was investigated using content and colorimetric analysis. Light attenuation measurements [2] were performed in order to evaluate the amount of mini-tablets in the Wurster draft tube and to assess the dynamics of the system. Additionally, circulation time measurements are being performed in order to better explain the cause of the coating variability.

Light attenuation measurement setup and coated mini-tablets.


**80. INVESTIGATION OF AGGLOMERATE BREAKAGE USING 3D PRINTING AND DEM MODELLING METHOD**

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Agglomerate breakage is a very common phenomenon in industry. Due to the complexity of breakage behaviour, there is a lack of a universally accepted model to quantify the agglomerate breakage propensity.

In this research, a Stratasys Objet 500 PolyJet 3D printer was used to produce test agglomerates with tuneable properties. The agglomerates had a number of 4 mm diameter rigid primary particles connected by either rigid or rubber like cylindrical inter particle bonds. Using this method, the agglomerate structure and inter particle bond properties can be precisely controlled and replicated. Quasi-static compression tests were performed for the agglomerates of each type. A Distinct Element Method (DEM) simulation of the agglomerate crushing was produced using the Timoshenko Beam Bond Model (TBBM) [1] to simulate the compression of agglomerates with mechanical properties matching the 3D printed agglomerate structures. For both agglomerate structures, the simulation and experiment show similar breakage patterns. However, simulation results significantly underestimated the compressive loads of agglomerates with rubber bonds. To improve simulations of compressive granule breakage, the influence of bond geometry and non-linear behaviour of the bond material needs to be considered.

![Randomly structured agglomerate breakage under compressive loading](image1.png)

(a) (b)

Randomly structured agglomerate breakage under compressive loading (a. agglomerate design before compression b. DEM of simulated breakage after compression).

During a ball milling process, particles are subjected to high stresses that in addition to particle size reduction also may induce solid state changes, such as the formation of an amorphous phase. Thus, in order to understand how milling operations should be designed to obtain the desired product of the processed particles, in terms of size and amorphisation of particles, an improved understanding of milling operation conditions are important.

In this study, two qualities of α-lactose monohydrate with different labelled particle size, 200M and 450M were milled in a planetary ball mill for different milling times with balls with diameter of 1, 5 and 10 mm. Ball-to-powder mass ratio of 25:1, 13:1 and 6:1 were used. The particle size distributions of the samples were measured using laser diffraction and the apparent amorphous content was determined using Raman spectroscopy [1].

Using ball-to-powder mass ratio of 25:1 gave the most effective milling which resulted in a particle size of ~5 μm during early stage of milling and highest degree of apparent amorphous content (82%) during later stage of milling. An increased milling time, gave a higher degree of apparent amorphous content. The larger balls showed minor degree of amorphisation when ball-to-powder mass ratio of 25:1 was used. The size reduction rate and rate of amorphicity were controlled by the number of collisions and the stress level of the inter-particulate collisions. It was hypothesized that the type of contact process, i.e. impact or sliding may control the degree of apparent amorphous content during a milling process.

The effect of ball to powder mass ratio (A) and ball diameter (B) on the degree of apparent amorphous content of lactose.

The aim of this study was to apply a quality by design (QbD) approach based on design of experiments as a risk-based proactive methodology to determine critical quality attributes (CQAs) of a twin screw granulation (TSG) process for controlled release tablets of a hydrolysable API.

A co-rotating twin screw extruder (TSE) (11mm process, ThermoFisher) with a volumetric feeder was used for granulation of the hydrolysable API. The blend consisted of a controlled release polymer along with the other excipients to aid granulation process in a twin screw extruder. A $2^3$ factorial design was used to investigate the effect of process parameters on the critical quality attributes of the granules. The process parameters were screw configuration, barrel zone temperature and feed rate. The quality attributes evaluated were particle size distribution, drug release and API crystallinity. Multiple linear regression analysis and ANOVA were employed. A model was generated for particle size prediction as well as that for drug release. TSG processed granules were characterized by DSC to confirm the crystallinity of the drug after processing within the extruder. The optimized granules were then converted into two dosage forms. Firstly they were filled into capsules and secondly the granules were compressed into tablets with a compression force of 2000 psi.

The modified screw configuration, low barrel temperature ranges and low feeding rate enabled desired particle size granules to be obtained from the extruder. In vitro release data (Figure 1.) for tablets demonstrated controlled release of API for up to 15.5 h. For all the formulations, 100% drug release was achieved but at different time points.

QbD approach was successfully used in the preparation of controlled release tablets via a twin-screw granulation process. Free flowing granules with angle of repose of 25 and 100% drug release from the tablets were achieved over the period of 15.5 h. The optimized formulation was able to achieve the set target goals of CQAs. TSG technique is remarkable in terms of its overall simplicity and continuous manufacturing mode.

![Drug release profile](image.png)
Wet granulation is often used in the pharmaceutical industry to improve powder characteristics for use in tabletting. The composition and microstructure of granular aggregates have a complex effect on granule mechanical properties, impacting tabletting and product performance. In tabletting, granule density and granule strength, affect powder re-arrangement, deformation and fragmentation of the granule. The granule microstructure also impacts water uptake, disintegration and subsequent dissolution. Hence, a pharmaceutical granulation can directly impact tabletting and product performance.

The impact of granule density in high-shear wet granulation at a typical production scale on tabletting and product performance was investigated. The impact of granule density on tabletting was rationalised with compressibility (solid fraction vs. compaction pressure), tabletability (tensile strength vs. compaction pressure) and compactability (tensile strength vs. solid fraction). Granule density impacted tabletability and compactability while product performance (disintegration and dissolution) was found to be impacted by solid fraction only. Hence, method of granulation and granule density should be a key consideration in product and manufacturing process design because of their potential impact on tablet compaction.
Fluidized bed granulation and drying process operated under partial vacuum conditions is an alternative to expensive freeze drying process in the formulation of thermo-sensitive substances in the food and pharmaceutical industry. An important process parameter in fluidized bed granulation is the configuration of the suspension spray system in the chamber. An optimal liquid suspension atomization is crucial in achieving a stable and successful granulation process. The expansion of the spray droplets, also termed as the spray zone [1], is affected by the operating conditions in the bed. Optimal adjustment of the spray zone is desirable to avoid wet-quenching of the particle bed or insufficient coverage of the fluidized particles with spray liquid. Although the development of spray zone in a fluidized bed has been studied for varying process parameters [1], the effect of operating pressure on the same has not been extensively investigated, which forms the motivation of this work.

The influence of operating pressure on the expansion of the spray zone for inert particles was investigated using the Euler-Lagrange discrete phase model in our previous study [2]. A significant influence of operating pressure on the impingement momentum and spread of the spray droplets was observed [2]. However, in addition to these spray characteristics, the evaporation rate of the liquid is also influenced by the pressure, which implies thermal stresses in the bioactive material especially for smaller spray droplets even before their contact with the fluidized particles. In this contribution non-inert droplets are simulated to include the heat and mass transfer characteristics between the air and droplet phases.

The simulation setup consists of a 3D fluidized bed chamber with a top-spray configuration. A single phase pressure nozzle is modelled with both one- and two-way coupling between the liquid and gas phase. Process parameters such as the droplet diameter, spray rate of liquid as well as the inlet air temperature and velocity are varied. Influence of sub-atmospheric pressure on the spray characteristics such as the droplet temperature, diameter, residence time, as well as the impingement length, velocity and volume of spray zone is obtained from the simulation results. The spatial and temporal distribution of these characteristics is compared for atmospheric pressure conditions as well as with empirical correlations. The study of these spray characteristics would further have a significant impact on the design of the spray nozzle as well as its location in fluidized beds operated under reduced pressure.


85. INVESTIGATION OF THE EFFECT OF MATERIAL PROPERTIES AND SCREW GEOMETRY ON THE PERFORMANCE OF TWIN SCREW GRANULATION

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Twin screw granulation is becoming increasingly relevant due to its compact size, continuous and robust mode of operation, flexible and customizable design, and flexible production capacity. Granule breakage has been shown to be an important rate process in twin screw granulation.

This work describes the experimental study undertaken to understand the breakage rate process in different types of screw elements in the twin screw granulator. Model powders of different particle sizes and model binders of different viscosity were chosen such that the mixtures gave a wide range of dynamic yield strength values. Cylindrical pellets were prepared from these model material mixtures and breakage specific experiments were conducted in the twin screw granulator using different designs of screw elements. The study was focused on understanding the breakage mechanism in conveying and distributive mixing elements. The breakage probability and the daughter size distribution were measured for the two screw element designs. It was found that the breakage in both, the distributive mixing elements and conveying elements, is a strong function of the dynamic yield strength of the powder-binder system and the granule size. The distributive mixing elements and the conveying elements follow two distinct breakage mechanisms that govern the final granule size distribution. A CAD geometry analysis of the free volume in the granulator revealed that there is a direct quantitative correlation between the screw geometry and the maximum granule size obtained in a twin screw wet granulation process of real formulations.

This work highlights the importance of rate-process specific fundamental experiments and relevance to real powder formulation behavior in twin screw granulation.
**86. DEVELOPMENT OF REGIME MAP FOR CONTINUOUS TWIN-SCREW WET GRANULATION**

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Wet granulation using twin screw extruder is a promising continuous technique for granulation of pharmaceutical formulations. Despite its superior characteristics compared to other granulation techniques such as flexibility and continuous process, the underlying phenomena and mechanisms associated with twin-screw granulation are not well understood yet. Recently, some research groups have investigated the regime map approach in order to develop a design space for continuous pharmaceutical manufacturing. The studies usually involve development of regime or process map, to understand the effect of process and equipment parameters for twin-screw granulation [1, 2]. The challenge is that these regime maps are limited to the equipment and formulation used in the experiments, and cannot be generalized for various applications. The present study deals with development of a preliminary regime map to understand the granule properties changes during continuous wet granulation. The regime map considers formulation properties, process parameters, and equipment parameters as input and granule properties as output. The granule properties in this study include granule size distribution (GSD), porosity, and liquid content which are critical quality attributes of granules in a tabletting unit.

Various formulations, screw configurations, extruder diameters, and process parameters are taken into account to develop the regime map by appropriate design of experiments. Different pharmaceutical formulations including microcrystalline cellulose (MCC)/Lactose/API are granulated in a 12 & 5 mm twin screw extruder (ThreeTec, Switzerland) with a length-to-diameter ratio of 40. The screws are configured at different geometries. Water is used as the granulating liquid, and process parameter, i.e. liquid-to-solid ratio, screw speed, and material throughput was changed on-the-fly. The resultant granule size distribution are measured using sieve analysis. The liquid content of granules is measured by adding dye into the liquid binder and quantifying the dye concentration in each granule size.


Continuous manufacturing (CM) is a recent approach in pharmaceutical production. It offers several advantages compared to the classical batch processing, such as minimal manual handling, higher efficiency and consistent quality [1]. The usage of Process Analytical Technology (PAT) tools is inevitable for process monitoring and continuous verification.

The CM line (L.B. Bohle, Ennigerloh, Germany) was operated with a throughput of 25 kg/h. The unit operations were continuous powder feeding, blending, direct compression and tablet dedusting. After a relaxation time of 20 min, which was determined before, the tablets were coated in subbatches (A-H) of 15 kg in order to realise the throughput.

The focus of this work was the coating step, which was monitored in-line using Raman spectroscopy as a PAT tool. In each experiment, 15 kg of round, 8 mm biconvex tablets with a mean mass of 193 mg were coated with an aqueous suspension of 17 % (w/w) Opadry® II beige in a KOCO 25 pan coater. The coating was performed with a spray rate of 120 g/min until 3 % weight gain.

Using the PLS method, a calibration model was built based on dataset F and one main component with a $R^2$ of 0.992 and a $Q^2$ of 0.991. The data of the remaining experiments were used as a test set for the model to predict the process progress. The observed versus predicted masses of the aqueous coating suspension are shown in figure 1. It was possible to monitor the process and to determine the coating endpoint with an uncertainty of one minute corresponding to a RMSEP of not more than 130 g of applied suspension.

![Figure 1. Observed vs predicted mass of coating suspension.](image-url)


Acknowledgement: L.B. Bohle Maschinen + Verfahren GmbH for supporting the study.
Roll compaction/dry granulation (RCDG) is a frequently used technique for the enlargement of particle size. In order to achieve high-quality granules, plastic deformation behaviour of raw materials is beneficial. Therefore isomalt, was chosen as a model material. This study focused on the evaluation of the influence of raw materials morphology on properties of produced granules and tablets. Thus, a milled grade (IM A), a grade consisting of sieved particles (IM B) and an agglomerated grade (IM C) were included.

Granulation was performed on a Gerteis Minipactor. Different specific compaction forces were applied. All other parameters were kept constant. Particle size distribution and specific surface areas were measured for all materials. During tableting internal lubrication was used.

Granulation led in cases of IM A and C to a strong enlargement in particle size. Granule size distribution became very similar at higher specific compaction forces. For IM B, granulation led only to a small increase in the particle size. Specific surface areas increased in all cases during RCDG in comparison to raw materials and decreased again by raising the specific compaction force but remained above raw material's surface area. Tabletability showed in all three cases reduced tablet strength with increased specific compaction forces. Figure 1 shows the plot of IM A exemplarily. The differences between tablets out of granules produced at 3 kN/cm and 6 kN/cm was small. Differences between 9 kN/cm and 12 kN/cm occurrec at pressures above 150 MPa. In comparison, granules of IM C, gave the hardest tablets up to a pressure of 140 MPa. Above that limit no differences to IM A granules were obvious. It may be assumed that higher pressure during RCDG as well as tabletting led to destruction of agglomerates and product properties are therefore determined by the primary particles. IM B granules resulted in the weakest tablets what is equal to its performance in direct compression [1].

![Figure 1. Tabletability of milled isomalt after dry granulation (mean ± sd, n = 10).](image)

MONITORING THE SEGREGATION OF AN OIL AND SUCROSE SUSPENSION AT DIFFERENT HUMIDITY CONDITIONS

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Many food products are suspensions containing hydrophilic particles within a continuous hydrophobic phase. A common example being peanut butter spread. The rheological attributes and visual form of suspensions can change considerably with the addition of small quantities of a secondary immiscible liquid. The reason for this has been ascribed to the favoured wetting properties of the secondary liquid and the solid particles.

The segregation of a suspension composed of a continuous lipid phase and hydrophilic particles under varying humidity conditions is examined. This was accomplished through non-destructive methods using X-ray computed tomography, optical methods as well as mass measurements. These approaches allowed the moisture migration within the suspension to be monitored with time during the storage of the sample.
EXPERIMENTAL INVESTIGATION OF VOLCANIC PARTICLES
AGGREGATION

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The large amount of fine ash released in the atmosphere by explosive volcanic eruptions constitutes a serious hazard to various economic and transport sectors (e.g. aviation) [1] and potentially to both human and animal health. Since most of the fine ash sediments in the form of aggregates, which commonly fall considerably faster than single particles, a quantitative understanding of aggregation mechanisms is of primary importance for an accurate estimation of ash concentration over time and space. Nevertheless, a complete understanding of these processes has not been achieved yet. The final goal of this work is to estimate the sticking probability of volcanic particles by filming a large amount of binary collisions. After filming the collisions with a high-speed camera, the sticking velocity was computed for both volcanic particles and silica spheres (between 20 μm and 150 μm) to investigate the effect of material and shape. In addition, several impact angles were tested to investigate the dependence of the restitution coefficient on the impact parameter [6].

Particles which are difficult to handle in fluidized beds due to their size distribution or surface properties can be fluidized in spouted beds. In the regarded prismatic spouted bed, a two-fluid nozzle is installed in bottom-spray configuration for coating purposes. The particles are entrained and accelerated in the so-called spout zone until reaching the fountain zone. Due to increasing cross sectional area of the process chamber, the particle velocity decreases with increasing chamber height whereby the particles fall down back into the annulus zone. The flow pattern is more structured than in a fluidized bed and heat, mass and momentum transfer are improved.

In this work, the residence times of particles in the different regions were investigated with a CFD-DEM approach [1]. With the results a circulation frequency could be determined and compared for several different process conditions. The simulations were performed with the original apparatus geometry and with a process chamber with installed draft plates which in former investigations had been found to have a positive influence on the spouting stability. Additionally, a spray zone above the nozzle was implemented and the residence times of the particles in this zone were calculated with a self-written post-processing tool. The results were compared with experiments in which a coating suspension with dye was injected and the time-dependent colour values of the particles were analysed with an image processing tool. A coarse-graining approach was used, in which several particles are represented by parcels [2].

Figure 1. CFD-DEM simulation of instantaneous particle positions and particle velocity distribution in a spouted bed without (left) and with (right) draft plates and schema of liquid injection via two-fluid nozzle in bottom-spray configuration.


The layering of a solution or a suspension of an active pharmaceutical ingredient (API) onto a porous or non-porous inert core in a fluidised bed is an alternative approach to wet granulation or extrusion-spheronisation processes in the case of low-dose, high-potent APIs. The deposition of an additional layer on top of the API may sometimes be required in order to achieve taste-masking, to protect the API from atmospheric effects, or to moderate the dissolution rate (e.g. entero-solvent formulations). A critical quality attribute of the final product is the uniformity of the coating layer, both at the level of a single pellet, and within the batch.

A chemical engineering description of the fluid bed coating process requires an understanding of the interplay between the wetting, imbition and evaporation rates of the coating fluid on individual pellets, together with phenomena such as aggregation and attrition of the pellets as well as the rates of heat- and mass-transfer between the pellets and the fluidising gas. Depending on the fluid bed design (e.g. Wurster insert, spouted bed) and nozzle position (e.g. top spray, bottom spray), the flow pattern of the gas and the solids in the bed is also of interest. To couple the single pellet heat and mass balance with that of the entire fluid bed, the residence time distribution in various parts of the fluid bed and also the mass and heat transfer coefficients have to be evaluated.

In this work, we present a mathematical model of a Wurster fluidized bed coating process and its experimental validation. The values of heat- and mass-transfer coefficients were evaluated as function of the superficial gas velocity using transient and steady-state experiments without any spray-on and with spraying pure solvent. Then, the single pellet wetting and drying models of the desired API suspension and/or coating solution were independently developed and validated. Finally, the whole process mass and enthalpy balances were coupled with the single pellet models to evaluate various operation scenarios, assess the process parametric sensitivity and robustness according to the QbD (Quality by Design) philosophy.
In wet granulation and agglomeration, liquid and/or paste with high viscosity is sometimes used where the viscosity is more than 1000 times higher than that of water. In those systems, viscous forces are exerted on particles through liquid bridges which have a tremendous impact on the powder behaviour in a granulator. In addition, many of the high viscosity liquids and pastes used in industry are non-Newtonian where the rheology is often characterised with the power-law. Therefore, it is of paramount importance to evaluate the viscous forces acting on particles to understand the granulation mechanisms and optimise the process.

In the present work, the Volume of Fluid (VOF) method is employed to carry out Direct Numerical Simulation (DNS) of a liquid bridge with power-law fluid, i.e. pendular liquid bridge formed between a pair of relatively moving particles, and the viscous forces acting on the particles are investigated. Furthermore, the simulation results are compared with the model in literature derived from the Reynolds lubrication theory.
Single drop impact of liquid on a static powder bed was studied to investigate the granule formation mechanism, droplet penetration time, as well as the characterization of granules (morphology and internal structure). Water was used as the liquid and two pharmaceutical powders, microcrystalline cellulose (MCC) and acetaminophen (APAP), were mixed to make heterogeneous powder beds. The complete drop impact and penetration was recorded by a high speed camera. Two granule formation mechanisms identified previously [1] occurred: Spreading and Tunneling. Spreading occurred for mixtures with an APAP amount of less than 30%, while Tunneling dominated when the APAP amount increased above 30%. With an increase of APAP concentration, the mean particle size decreased, drop penetration time increased, and the granules formed became smaller in size, which was in good agreement with a similar study [2]. The granule morphology and internal structure were characterized by a prism method with image analysis [1] and micro-CT, respectively. The Spreading mechanism always produced flat disks with a porous internal structure, while the Tunneling mechanism always produced round granules with a dense internal structure. It is believed that the mean particle size of the powder bed is the predominant factor in influencing the formation mechanism, drop penetration time, and granule properties.

Figure: a) The Spreading formation mechanism, b) granule side (left) and top (right) views, and c) micro-CT image of the internal structure of the granule.


High shear wet granulation (HSWG) is commonly used in the pharmaceutical industry to tailor the powder properties to the requirements of tableting. The effect of changes in the equipment, scale, or formulation are typically assessed on the attributes of dried granules or compressed tablets. Development of high (temporal) resolution in-line PATs that correlate well with end product Critical Quality Attributes (CQAs) is crucial to improve process understanding and monitor quality in-line.

The application of a drag flow force (DFF) sensor as a monitoring tool overcomes the limitations of other HSWG PATs while providing high frequency and high (temporal) resolution in-line granule densification data that correlates well with granule densification and tablet dissolution [1]. The DFF sensor is a thin, hollow cylindrical pin, whose deflection in the flow is measured by 2 optical strain gauges affixed at the inner surface of the pin. The sensor is calibrated to measure the DFF that is related to fundamental parameters of the material such as density and shear viscosity. In addition to force, the DFF sensor outputs temperature.

In these studies, the in-line response of the DFF sensor is correlated with at-line measurements of flow properties of the wet granules collected at different time points during processing and measured using an FT4 Powder Rheometer® [2]. This correlation allows better understanding of the DFF sensor response as representing fundamental properties of the granules which are known to directly impact tablet CQAs [2].

The drag flow force sensor (a) and changes in the Force Pulse Magnitude as a function of time.


Granules can be regarded as multi-phase composite materials with a complex internal structure that includes one or more type of primary particles, a binder, and porosity. When compressive or shear stress field is applied to a granule, it undergoes structural changes associated with particle rearrangement, deformation and ultimately breakage. Similar transformations of granule microstructure also occur during the dissolution of granules, as the individual primary particles and binder bridges are eroded proportionally to their dissolution rate. A weakened granule structure can undergo a series of breakage events during dissolution, which in turn affect the release profile of an active ingredient [1]. The ambition of the present work is to provide quantitatives relationship between granule microstructure, its mechanical strength in the dry state, and mechanism and extent of granule disintegration and breakage during dissolution.

Pharmaceutical granules have been prepared under different values of the Froude number in a high shear granulator in order to obtain a series with a constant composition but varying porosity. The inner structure of the granules was examinated by x-ray microtomography [2]. The stress-strain relationship of the granules was obtained from single-granule compression tests conducted on a Texture Analyzer. The experimental data were used for the validation of a DEM simulation of the compaction and breakage of virtual granules, and to calibrate material-related parameters of the model [3-5]. The structure and hardness data were then correlated with dissolution profiles in order to find a connection between the mechanical and dissolution properties of the granules.


Novel bio-based composite materials attract a lot of attention at the moment. In this work we have looked in combinations of starch, salt and water which under the right heating conditions form a very strong composite material which could be used for building purposes. By doing a design of experiments of the different variables of the composite material the strength of the material was assessed. Also the plastic and elastic deformation was studied. The composites material was optimized to the best strength possible and compared to other materials used for building.

This work showed that a remarkable new composite material was developed consisting of simple in nature available material could be easily made and showed good strength characteristics. The deformation under stress showed remarkable new insights.

These composites show unusual strength properties. The different strength properties will be identified and explained.

Examples of possible use of the material will be shown and discussed.
A good flowing behaviour is a key requirement for industrial food powders, and characterization of powder flowing is often needed for reliable design and proper operation of processes such as filling, packing or storage and discharge from silos. Flowability can be measured with a huge number of techniques, varying from single number tests (e.g. angle of repose, Carr index measurements) to ring shear test and powder rheometers. It is in any case necessary to correlate experimental data with processing experience, as flowability is no absolute property and the definition of good or poor flowing might differ depending on the desired application.

In the first part of this work we analysed several food powders, aiming at establishing correlations between powder characteristics such as shape, moisture or physical state and flowing behaviour. Based on the findings, we discuss how powder properties can be optimized during production process in order to improve flowing.

In the second part of the work we focused on the role of flowing agents, which are often used to improve behaviour of food powders for manufacturing purposes (e.g. filling, mixing, and packing). Free-flow agents can also inhibit or prevent lumping and caking so that the selection of the right material should take into account the specific needs of the final application. Previous study also suggested that the optimal amount of flowing agent to be added is a function of the surface coverage level [1].

The objective was to identify which properties of selected materials are more relevant to predict how suitable they are to improve flowing. Our findings suggested that the analysis of particle shape together with surface-to-volume ratio might be a useful indicator of the efficacy of a potential flowing agent.

CONTINUOUS GRINDING OF SCRAP TIRE RUBBER PARTICLES IN FLUIDIZED-BED JET MILL

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The global automotive tire yield maintains a continuous growth for the civil and industrial’s requirements in recent years. When the tires are no longer safe to be used, they will become the solid waste and harm the environment. The recycling of waste tire rubber has attracted great attention due to efforts related to the prevention of environmental pollution and conservation of petroleum resource. Recently, recycling waste tire rubber by powder technologies is widely considered as a promising recycling method.

In this work, the scrap tire rubber particles were ground in a fluidized-bed jet mill under various operating parameters, such as inlet gas pressure, feed rate and rotating speed of classifier. The influence of the operating parameters on the performance of the continuous grinding of tire rubber particles at ambient and cryogenic temperature was investigated. It is found that for the ambient continuous grinding the volume mean diameter $d(4, 3)$ of the products decreased with the increase of inlet gas pressure and rotating speed of classifier, while it decreased firstly and increased then with the increase of the feed rate. The volume mean diameter $d(4, 3)$ reached minimum value of 109.7 μm at feed rate of 15.4 g/min, inlet gas pressure of 0.6 MPa and rotating speed of 1800 rpm in the ambient continuous grinding. However, for the cryogenic continuous grinding, the minimum volume mean diameter $d(4, 3)$ of products was 65.3 μm at feed rate of 19.2 g/min, inlet pressure of 0.6 MPa and rotating speed of 2400 rpm. According to the SEM photographs, it is clear that the particle size obviously declined for the continuous grinding at cryogenic temperature. The products obtained by ambient continuous grinding were smooth and covered by some fine particles, whereas the particles ground at cryogenic temperature were irregular with sharp edges.

SEM photographs of particles after continuous grinding.
The study of particle transport in porous media is of great significance in pollutant treatment, grouting reinforcement, municipal solid waste landfills and groundwater exploitation. An analytical solution of a corrected convection-dispersion model that takes into account dispersive flux on the deposition kinetic was obtained for particle concentration decay types. Rationality and accuracy of the solution were verified from the time, distance, deposition coefficient, diffusion coefficient and decay coefficient. As the time increased, the particle concentration increased from zero to the peak value, and then the particle concentration decreased to zero. However, with the increase of distance, the peak value of the particle concentration gradually decreased. Second, the deposition coefficient not only affected the magnitude of the peak value but also influenced the distance corresponding to the peak value. In addition, the greater the attenuation coefficient, the smaller the peak value appeared. In general, the predicted results of the solution that considers dispersive flux on the deposition kinetic were smaller than when the dispersion flux was not considered.
For most powdered products in the food industry, a quick and complete reconstitution is vital to product quality. However poor reconstitution remains one of the greatest consumer complaints faced by the food industry, and reconstitution problems pose issues for a great number of other industries as well, such as the pharmaceutical, detergent, and chemical manufacturers. As explained by Forny et al. [1], reconstitution should not only be thought of as dissolution, but in fact encompasses a number of simultaneously-occurring physical phenomena, such as wetting, capillarity, submergence, dispersing, and (for some, but not all food components), dissolution.

When powders are added to the surface of a liquid, they must submerge below the surface in order for dispersion and dissolution to occur; however, this step in itself can be rate-limiting [2], leading to the formation of heaps of powder evolving into floating layers - this quality defect can particularly be exacerbated if there is swelling of the food components, leading to the collapse of the internal pore network and thus reduced capillarity.

Schubert [3] explained that if the surface tension of the liquid is too high, and particularly if the particle has a hydrophobic surface, then a particle (even a heavy one), can remain at the liquid surface due to the action of capillary forces - this has been explained mathematically as well [4]. According to this logic, then a decrease in surface tension should lead to improved particle sinking; however, Schubert did not consider the effect of surface tension on capillary liquid penetration. As predicted by the Washburn Equation [5], capillary penetration is favoured by a high surface tension. In the current presentation, we demonstrate the effects surface tension actually play in the overall reconstitution of powders in water, by using surfactants to modify the liquid properties.

Moreover, it will be demonstrated that how the positioning of a surfactant on the surface of particles, rather than into the liquid medium, affects the wetting properties (by altering the contact angle between the liquid and solid surfaces), as well as the dispersing of powders. Reconstitution experiments are performed in an agitated vessel equipped with an FBRM (Focused Beam Reflectance Measurement) probe. This probe, which is positioned such as not to disturb the liquid flow, is able to track the distribution of chord lengths (related to particle size), and is thus able to directly follow the dispersing behaviour of agglomerates and particle aggregates. Results reveal that a competition of competing physical phenomena determine the overall effect that surface tension has on reconstitution quality.


**102. DIRECT NUMERICAL SIMULATIONS OF PARTICLE COLLISIONS ON WET SURFACE**

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Detailed knowledge of micro-mechanics of individual particle collisions in the presence of liquid is crucial for modelling/understanding wet granular flows that are omnipresent in nature and various industries. In this work, direct numerical simulations were conducted to study the influence of the interstitial fluid on the collision mechanics, using a combined model of the volume-of-fluid and the immersed boundary method. The impact of spheres on a surface covered by a liquid layer was simulated, focusing on collision details such as the dynamic formation of a liquid bridge, as well as the kinetic motion of the particle. It is demonstrated that our model can well reproduce the phenomena observed experimentally during the complete collision process (as shown in Figure 1): penetration of particle into liquid layer, contact of particle with the wall, emergence of particle, as well as formation, thinning and rupture of the liquid bridge. Furthermore, the wet restitution coefficients, which characterize the energy dissipation during collisions, predicted by the simulations agree quantitatively with the results measured from experiments. Subsequently, different simulations were performed to study the relevance of collision parameters on the overall collision behaviour. It is revealed that the wet restitution coefficient strongly depends on the impact velocity, liquid viscosity, layer thickness, and particle size, but is only slightly affected by the surface tension coefficient of the liquid.

![Figure 1](image-url). Normal impact of a 1.74mm sphere on a 400µm water layer at an impact velocity of 1.13 m/s: experimental high-speed recording images (top) and simulation snapshots (bottom).

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In this paper, industrial fuel powders including bitumite, ignite and petroleum coke, were selected as research materials. The influence of humidity on surface energetic and flow behavior of fuel powders was investigated. Both of the surface and the bulk flow properties of fuel particle materials were determined at dry and RH 90% environmental conditions. The surface energy was determined using surface energy analyzer, and bulk flow properties were measured in terms of angle of internal friction using a powder flow tester. The surface energy of all fuel powders was mostly determined by long range dispersive interactions. The bitumite has the highest dispersive surface energy while the lignite has the highest specific surface energy. The petroleum coke shows an extremely low polarity character. Furthermore, it indicated that the homogeneity of the fuel particle surfaces is increased as the increase of ambient humidity. In particular, for hydrophilic lignite particles, the increase of surface homogeneity is more significant. Detailed analysis showed that surface energy as well as surface energy distribution can be effective indicators for flow behavior of fuel powders under varying humid conditions.
The effect of water on the surface energy, bulk and flow properties of lignite was experimentally investigated. Using a FT4 Powder Rheometer, changes in bulk properties were collected as a function of water content (0%, 5%, 10%, 15%, 20%). The interactions among coal particles and polar or non-polar gaseous probes were investigated using an inverse gas chromatography technique. The results show that water content plays a significant role on the packing and flowing of the particles, as well as the surface energy. Small amounts of water created porous aggregates due to liquid bridging. Greater amounts of water resulted in the filling of the void-spaces. This was indicated by an increase in basic flow energy, density and pressure drop with a decrease in porosity and surface energy. A classification of water form between coal particles was proposed based on Campbell’s work[1], indicating that different water formed had different influence on the flowability and surface energy on lignite particle and resulted different particle force on microscale and flow properties on macroscale. In the end, a model was developed to relate the surface energy from the microscale with shear test data and bulk properties on the macroscale. This model was used to predict how the different water content level would influence the surface energy of particle and what the flowability of the tested powder would be under different water content circumstances. What’s more, this model would give the interaction of particle with different water content. This result was compared with that obtained from the IGC data and showed good agreement.

Impact of Raw Material Variability upon Continuous Twin Screw Granulation

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(Uncontrolled) raw material variability is a major challenge for pharmaceutical processing. Due to the need for fast time to market and since only low quantities of active pharmaceutical ingredients (API) are available for process development, the impact of raw material variability is usually insufficiently studied. However, changes in API synthesis process or suppliers are common during the product life cycle. These changes can strongly impact the API properties (e.g. particle size distribution, surface properties) with potential repercussion upon the product manufacturing process and the product quality. Expensive and time-consuming process redevelopment is then necessary to manage new API properties generated by these changes, without however building the knowledge around the impact of the API properties upon the process in a systematic approach. This is a reason why recent literature [1] and international guidance [2-3] highlighted the need for a global and multi-scale approach to understand the link between raw material properties, raw material variability, process and product specifications.

In this work, the influence of raw material variability upon a continuous twin-screw granulation process is studied. In a first step, several API batches (i.e., starting powders for drug product manufacturing) were characterised in detail using 14 different raw material characterization techniques to understand the batch-to-batch variability. Therefore, all obtained characterization data were analysed using principal component analysis (PCA). The PCA allowed to highlight three main super properties (i.e., principal components) responsible for the differences between the API batches: the particle size and related properties, the span and powder packing properties and the surface related properties. In a second step, these material attributes responsible for the differences between the API batches (i.e., the principal components) were included as factor in a D-optimal design to study the impact of these together with twin-screw granulation process parameters upon critical granule quality attributes (granules size distribution and friability). The results showed a larger impact of the liquid to solid ratio and of the API properties compared to other process parameters. The design results allowed then to define the process design space which is able to manage the observed API material variability leading to similar granule quality attributes for the different API batches.


ESTIMATION OF COEFFICIENT OF RESTITUTION OF IRREGULAR SHAPED PARTICLES ON HORIZONTAL SUBSTRATES

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The coefficient of restitution is one of the fundamental particle properties, which is required in the modelling of complex granular flows with strong particle-particle interactions. Therefore, experimental measurements of the coefficient of restitution are significant in increasing the accuracy of multi-scale simulations involved particle interactions (such as CFD-DEM, Two-fluid and Monte-Carlo approaches). Moreover, particles are irregular shaped in almost all industrial applications.

In this work, the coefficient of restitution of maltodextrin particles with three dextrose equivalent values (Group A, irregular shaped) on horizontal maltodextrin and glass substrates are measured by high speed imaging system. Accounting for the fine particle size, a small group of particles is dropped using a vibratory feeder. The impact velocity of particles is controlled by adjusting the height and the amplitude of oscillation of the feeder. Further, the intensity calibration is used to avoid movements of particles out of two-dimensional observation plane, which caused by the particle release approach and the random rebounds of irregular shaped particles. With the help of particle tracking velocimetry (PTV) method [1], the trajectories of a group of particles can be simultaneously tracked to evaluate the coefficient of restitution of individual particles.

Discrete element method (DEM) is used to simulate the impacting of irregular shaped particles on horizontal substrates based on the multi-sphere model [2, 3], where the shape of maltodextrin particle reconstructed by experimental measurements. The measured coefficient of restitution of maltodextrin particles is used in the DEM simulation. Compared with PTV measurements, influences of different contact models on impact behaviours are discussed.


Nowadays, there is a strong need for a further step to be taken towards the development of a cost-effective product that meets the stringent regulations that are being imposed on most industries. Such a step is very important but represents a non-trivial task, particularly in those industries where, for instance granulation is defined as being a unit operation of the production process; this being due to the complex nature of the granulation process itself. Consequently, developing a fast, accurate, transparent and cost-effective predictive model is a target that researchers in both industry and academia strive to achieve. Various approaches have hitherto been utilized to model the process such as population balance models and neural networks [1-2]. However, these modelling approaches cannot effectively deal with the uncertainties present in both the inputs and the outputs of the granulation process systematically. Such uncertainties may be due to measurement errors or constraints, or simply to the heterogeneous distribution of both porosity and binder content during the granulation process. In this research, a type-2 fuzzy modelling paradigm has been implemented to predict the properties of the granules produced by a high shear granulation process and also to absorb the uncertainties that surround the process. This choice was motivated by the fact that fuzzy logic can absorb uncertainties more naturally and can approximate behaviour using a simple and yet effective formalism. In addition, such a model has been utilized to extract meaningful information to describe the process linguistically in a simple way that can be understood by users. In order to take account of any unmodelled stochastic behaviour of the process, and also to improve the prediction performance, a Gaussian mixture model has been used. Experimental results show that the proposed predictive model was successful in predicting the properties of the granules accurately with the added advantage of the modelling framework being more transparent.


Rotating drums play an important role in industry for mixing, milling, coating and drying processes. Radial segregation in a mixture has received extensive studies. However, most of the studies focus on the size- or density-induced segregation of spherical particles. For example, Eskin et al. [1] studied the radial segregation of binary mixtures in a rotating drum by means of mathematical model. Yamamoto et al. [2] used DEM to investigate the density effect for mixing behaviour in a rotating drum. Jain et al. [3] studied the regimes of mixing and segregation in combined size and density granular system experimentally. They found that mixing can be achieved instead of segregation if the denser beads are larger or particle size ratio is greater than the density ratio. But the difference in particle shape alone could also incur segregation. Though a few studies have focused on the particle shape effect on segregation [4, 5], e.g., the streak formation of particles deferring in size, density and blockiness, the segregation induced by shape individually in the mixture of ellipsoids have not been studied yet.

In this work, simulation with discrete element method (DEM) is implemented to study the radial segregation of the binary mixture of ellipsoidal particles in a rotating drum. The segregation patterns of the mixture of spheres and oblate spheroids or spheres and prolate spheroids are presented. The effects of rotating speed on the degree of segregation in a steady state are investigated. The results show that, for either the binary mixture of spheres and oblate spheroids or spheres and prolate spheroids, ellipsoids tend to distribute in the periphery of the bed in a state of equilibrium, while spherical particles are more likely to accumulate in the core region. In addition, when the rotating speed increases from 10 rpm to 30 rpm, the degree of segregation reduces evidently for each case.


The abstract outlines a pilot scale research facility for granulation of high value products at Centre for Process Innovation (CPI). CPI provides access to industry trained experts and open access facilities which enable the formulating industries to develop and scale up advanced formulated products productively, efficiently, and with less risk. Currently CPI has a continuous powder mixing and measurement pilot plant facility that is capable processing up to 2500 kg/h. A powder packaging and filling research line and granulation facilities are being established at the National Formulation Centre of CPI. Formulation processes typically involve a series of processing steps ranging from mixing, particle size manipulation, compaction, fluidisation, conveying and filling into bins/hoppers. Each process step typically results in a physical or chemical change to the material being processed. The intermediate products created by each processing step must be controlled in order to ensure the quality of the final product. Key quality attributes such as powder blend homogeneity, shape and size of the granules and flowability are still major challenges which limit the efficiency of many manufacturing processes. There is no standard protocol or procedure for in-line process parameter monitoring and measurement. The approach adopted in the pharmaceutical industry is the application of Process Analytical Technology (PAT). PAT is "a system for designing, analysing, and controlling manufacturing through timely measurements (i.e., during processing) of critical quality and performance attributes of raw and in-process materials and processes with the goal of ensuring final product quality." PAT is becoming a very important tool for designing and controlling pharmaceutical processes and is starting to be adopted within the industry. The facility will be useful to investigate the performance of powder processing equipment through the application of on-line measurement technologies. The pilot scale facility would be ideal for industries and academic research groups to use for process development, scale up, optimisation and troubleshooting.
CONTINUOUS MELT CO-CRYSTALLIZATION OF NOVEL THEOPHYLLINE AND 4-AMINOBENZOIC ACID CO-CRYSTALS FROM TWIN SCREW MELT GRANULATION PROCESS

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Recently, increased demand for greener and more environmentally sustainable processes has focused the attention on mechano-chemical process. Mechano-chemical synthesis is one in which solid reactants are vigorously ground (milling or grinding) together with minimal or even no solvent. Mechano-chemical synthesis is environmentally friendly, easy, cheap, fast reaction rates and high yields; these advantageous properties made mechano-chemical synthesis a method of choice for co-crystal formation. Pharmaceutical co-crystals are solids that are crystalline materials comprise of two or more components held together by non-covalent forces. In recent years co-crystals are being studied intensively due to the potential for improved pharmaceutical properties such as increased solubility, bioavailability, chemical stability and hygroscopicity of active pharmaceutical ingredients.

High-shear granulation and twin screw extrusion, have recently been used for co-crystal preparation. These methods are environmentally friendly as they avoid, or minimise, the use of organic solvents. Twin screw extruder mediated co-crystallisation is a promising processing technique for continuous co-crystallisation. Although twin screw extruder mediated co-crystallisation has been reported with various primary experimental parameters (screw geometry, temperature, feed rate and the RPM of the screws) that can affect co-crystal conversion. However co-crystallisation with tablet excipients was not extensively studied. Therefore to enhance understanding of co-crystallisation process with melt granulation in the present study for the first time investigated the suitability of different polymeric binders for continuous melt co-crystallization.

A Theophylline-4-Aminobenzoic acid novel co-crystal forming system was selected for the study. Appropriate stoichiometric ratios of Theophylline-4-Aminobenzoic acid were prepared. Melt co-crystallization of novel co-crystal system was carried out in a co-rotating 12 mm Hybrid Mini-Extruder (Three-Tec GmbH, Switzerland) with a length-to-diameter ratio of 40:1. The melt granulated samples were mainly characterised by powder X-ray diffraction (PXRPD), differential scanning calorimetry (DSC), thermogravimetric analysis (TGA), physical and mechanical properties of co-crystals and tabletability of co-crystal powders. As shown melt binders had a significant influence on co-crystallization process and co-crystal powder compatibility, consequently they are important to consider in co-crystallization process. Finally twin screw melt granulation mediated co-crystallisation process can be considered to be continuous production of drug product co-crystals formulation.
Twin screw wet granulation (TSWG) is an emerging continuous process capable of producing granules at lower liquid quantity and with better consistency than found by a high shear batch mixer. For these reasons TSWG could potentially replace the present batch granulation technology making the process more reproducible and cost-effective [1,2]. The successful exploitation of the new process cannot be however possible without a thorough understanding of the operational and system parameters affecting granule properties.

In this work we study the effect of different process variables, i.e. liquid-to-solid ratio, screw speed, and powder flow rate on particle size distribution (PSD) of granules (microcrystalline cellulose) obtained in a TSWG process. In addition, we investigate how different screw configurations (various combinations of conveying, cutting and kneading elements) influence the granulation outcome. A fractional (minimum runs) design of experiments (DoE) is employed to cover both main effects and secondary interactions of the variables considered. The granules are produced in a twin screw extruder with screw diameter 12 mm and length-to-diameter ratio 40:1 and characterized using both laser diffraction and microscopic techniques.


High-shear granulation, the agglomeration of small particles in heavy mixers to produce agglomerates called granules, is extensively used by many industries. The key mechanisms taking place during the granulation process, wetting and nucleation; consolidation and growth; and breakage and attrition, however, are not yet fully understood.

The aim of this work is to predict consolidation and layered growth by finding a correct model and validating the model with experimental data. In this work, two models are evaluated [1]. The first model assumes surface tension is the driving force for growth in a static situation. According to this model, growth occurs linearly with the square root of time. The second model, on the other hand, is based on deformation-driven diffusive growth, with small deformations causing a diffusion-like migration of binder liquid and powder. For this dynamic model, the growth rate decays exponentially until the granule has reached a final size, which depends on the initial amount of liquid and powder properties.

In order to properly monitor the growth of particles without the interference of other mechanisms such as breakage and attrition, a Consolidation-Only Granulator (COG) was designed. This granulator consists of a container that is rapidly moved back and forth on a rail, which allows for the determination of the exact number of impacts granules receive. Prenucleated granules were consolidated for set times and weighed. In this way, the growth of the granules could be monitored over time. Two different powder-binder systems were considered: lactose monohydrate and glass beads with silicone oils of various viscosities.

Of the two models, the first, static, model appears to best describe growth behaviour of the granules, although more growth was achieved compared to static experiments. This implies that surface tension is the driving force of layered growth, even in dynamic situations, and that movement only facilitates further densification.

The investigation of the drying of single micro droplets, which contain solids like salt or nanoparticles, is a challenging but very informative task to get information about structure formation and drying behaviors of powdered solids in a micro scaled range. These investigations are useful as pre-experiments for fluidized bed processes.

These fluidized bed processes are used to formulate high-quality granules with defined properties from liquid solutions or suspensions. Beside composition, the structure of the granules defines important properties such as dissolution rate, flow ability or strength. The structure is influenced by material parameters, but the process conditions such as temperature or humidity have also a very strong impact.

The solutions, which lead to solid layers or binding bridges between particles, are the most important components in all these processes. It is an indispensable condition to examine these solutions more intense by single droplet experiments. Therefore the drying of sessile solid-containing droplets with special attention to the three-dimensional analysis of the dried structures left on the substrates is determined.

Figure 1 shows the dried structures of sodium benzoate, with 5 and 30 wt-% solid content. Both droplets were dried under the same conditions. The formed structures are totally different to each other, which is seen at the height profiles as well as on the top view of the structures.

For realising drying experiments of sessile micro droplets a special drying chamber was constructed. The analysis of the dried structures is based on white-light interferometry provided by an additional simple Monte Carlo method. The influences of temperature, humidity, and volume flow rate, as well as the solid content in the droplet will be presented.
Experiment No. 1, $T_{ch} = 50^\circ C$, $V_{air} = 400$ ml/min, $Y_{in} = 3$ g/kg, $c_s = 5$ wt-%

Experiment No. 2, $T_{ch} = 50^\circ C$, $V_{air} = 400$ ml/min, $Y_{in} = 3$ g/kg, $c_s = 30$ wt-%

Figure 1. Influence of solid content on final structure (left selected experiment 1 out of 5, right: averaged height profile and error bars).
The purpose of this work was to develop multicompartmental pharmaceutical products enabling administration of both solid and liquid phase material into a single product. This could be achieved by filling the powder(s) and/or liquid(s) (solution/suspension) into different compartments inside a 3D printed geometry or by 3D printing molds for casting of liquid/semisolid material.

The 3D printed objects were designed using computer aided design (CAD) and 3D printed using fused deposition modeling (FDM), followed by manual filling of solid/liquid formulation components. The 3D printed compartmental products possessed high structural integrity assessed by crushing strength tests, however, compromised structural features could be identified with optical and scanning electron microscopy, as well as with X-ray micro computed tomography (XµCT). Drug release from each compartment of a 3D printed product can be tailor-made by simple geometric modifications. The proposed additive manufacturing approach circumvented the need for exposing the active pharmaceutical ingredients (APIs) to elevated temperatures and high mechanical forces, as it is common during hot-melt extrusion and tableting. Furthermore, the proposed 3D printing method encompass that a change of formulation composition can be performed without influencing the performance of 3D printing process, because the APIs together with different excipients in powder or liquid phase are not 3D printed.

This work is paving the way towards manufacturing of complex pharmaceutical products with multiple APIs and a possibility to isolate formulation components from each other. This approach will enable designing of innovative pharmaceutical products meeting the requirements of patient-oriented personalized medication.
Chemical looping reforming (CLR) and chemical looping combustion (CLC) are promising technologies with inherent CO$_2$ capture for transforming fuels into syngas and energy respectively. Circulating oxygen carriers (OC) are used to transfer oxygen from mostly air to the fuel inside the process. Over the past years a variety of materials have been proposed for the role of oxygen carriers, ranging from bulk mineral powders to oxygen carrier particles engineered for shape, size and composition. Iron based materials are very promising and cost effective candidates with minor impact on the environment as compared to the toxic Ni-based OCs.

Granulation by the industrial spray-drying technique is suitable for producing oxygen carrier particles with high sphericity and dimensions fit for the fluidized-bed reactors of the CL-process. The lifetime of the oxygen carriers in these reactors however strongly depends on their mechanical properties (as measured by the crushing strength and the attrition resistance) which is related with their morphology and porosity. As this morphology depends on the spray drying suspension, the relation between the additives used in the iron-based suspension and the morphology of the spray-dried particles is investigated in this work [1]. The influence of the concentration of the binder, dispersing agent and solids in the spray-drying suspensions and the intensity of the milling procedure on the morphology and microstructure of the resulting particles is studied by Hg-porosimetry, tapped density, optical microscopy and SEM. A controlled sintering treatment is used during post-processing of these spray-dried particles in order to further improve their mechanical properties before investigating their performance as oxygen carriers in the chemical looping process.

The use of interactive mixtures is one of the methods, how to achieve acceptable bioavailability of poorly soluble active pharmaceutical ingredients (API). The interactive powder mixtures are used mainly when any kind of chemical modification of API is not desirable due to registration or economic aspects, because they involve only physical processing of API. Preparation of interactive mixtures comprises micronizing for increasing the specific surface area and the dissolution rate of API. However, micronized substance itself tends to form clusters in the solvent so the effective wetted surface is reduced again. Fixing the API on the surface of larger excipient particles by preparation of the interactive mixture helps to overcome this problem and achieve large surface area being available for the dissolution. Therefore, the aim of this study was to prepare model interactive mixtures, find optimal parameters of particle components in order to achieve the lowest scale of homogeneity.

Doxazosin mesilate and ibuprofen were used as the model micronized active substances. As a carrier, dicalcium phosphate dihydrate (trade name Emcompress) and lactose monohydrate were used. The quality of prepared mixtures was assessed by the mixture homogeneity, using the relative standard deviation (RSD), which indicated whether the interaction between the drug and the carrier was achieved within the volume of the mixture. At first, the influence of the carrier type and particle size on the final homogeneity was studied. It was found that 125-250 μm fraction of Emcompress is the most convenient for the preparation of model interactive mixtures regarding to homogeneity. At second, the influence of the concentration of API on the final homogeneity was also studied. The best result was observed in the mixture containing 5% of doxazosin mesilate, which exhibited the lowest RSD value (0.82 %).

Moreover, the developed methodology for measuring the adhesion force by centrifugation method was used to explain how the interactions between particles affect the properties of the resulting mixture. The method involved depositing the micronized API onto the surface of a tablet prepared of the carrier material with controlled surface roughness, applying the centrifugal force to remove some of the particles from the carrier surface to a collector, and quantifying the amount of removed API using a HPLC analysis of the collector sample. The results showed that, the stronger the interaction between API and carrier, the better homogeneity of the resulting mixture. It was also confirmed by the results of surface energy measurements using the inverse gas chromatography. Suitable ratio of both components and particle size was also found to influence the homogeneity of the mixture.

Despite the results above, both using the inverse gas chromatography and the centrifugation method to measure the adhesive forces between the particles are extremely sensitive to proper deposition of an API monolayer onto the measured surface. Therefore, the experimental technique is in the process of ongoing development to improve the way, how to apply API onto the surface in the future centrifugal experiments. Furthermore, the application of optical and electron microscopy for measuring the number of deposited particles should further improve the process of obtaining accurate results.
Peroxide vapours can initiate oxidative reactions in dry systems. In powder detergents the stability of enzymes are decreased during storage, especially in powders with added bleach particles, and one reasonable hypothesis for this degradation has been oxidation processes due to the release of hydrogen peroxide from added bleach particles [1,2]. Thus, incorporation of a probe compound as a marker of peroxides in dry granular systems may be a relevant tool to follow the presence of damaging peroxides during storage.

Spectroscopic measurements, relying on chemical reaction, represent a quick detection technique which is widely used for chemical detection in solution. The techniques can be transferred into dry model systems and together with probe compounds, this may be an effective method for studying degradation in dry systems, also when temperature and humidity is changed.

Titanium salts are excellent colorimetric probes for the presence of hydrogen peroxide, since the Ti(IV) complexes react with hydrogen peroxide. The salts go from being colourless to bright yellow after reacting with hydrogen peroxide allowing the reaction to be followed visually or by UV-vis spectroscopy. Diphenyl-1-pyrenylphosphine (DPPP) is a non-fluorescent probe compound, which forms a fluorescent product when it reacts with hydrogen peroxide, thus allowing CLSM studies of peroxide reactions at a microscopic scale in granular particle mixtures.

The probe compounds were incorporated into powder model systems, and spectroscopic measurements have been used to measure the reaction products between the probe compounds and peroxides. A setup with a controlled partial pressure of hydrogen peroxide vapour was used in order to test the sensitivities of the probe compounds to detect peroxide vapours. Probe compounds absorbed onto particles were tested in the presence of peroxides in the model systems. The effect of the atmospheric humidity and temperature were also examined in the study.


The modular structure of the Glatt´s MODCOS continuous processing solution allows individual installation of each process unit according to the process or customer requirements. The simplest configuration of the MODCOS portfolio is a direct compression installation, which mainly consists of powder dosing, powder mixing, tabletting and analytical measuring devices. For an example, see picture below.

This case study covers the direct tabletting of API loaded and coated pellets in a powder matrix of excipients using this installation. Pellets and excipients were fed into the process by K-Tron dosing system. To ensure uniformity, the ingredients were mixed in the Glatt Continuous Dry Mixer (MODCOS DRY MIX) and compacted by the tablet press 102i supplied by Fette. To prevent damage to the pellets and ensure the required dissolution rate, a few modifications were necessary to the process equipment. This configuration, together with the adjusted settings, avoided separation and damage to the pellets, ensuring that homogeneous pellet content was reached during lengthy production runs.

Direct tabletting installation  
Chart: tablet mass and pellet mass with RSD
119. THEORETICAL AND EXPERIMENTAL STUDY ON WET GRANULATION REGIMES

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The purpose of this research was to analyse the influence surface liquid content on idealised materials (monosized glass beads and olivine sand). It is well-known that during wet granulation the liquid phase forms capillary bridges between near touching solid particles [1]. The state of such liquid bridges depends on the amount of liquid binder mixed into the system and has profound impact on the property of formed structures. The volume of liquid bridge before reaching funicular state is used when a liquid binder is mixed with the granular material considering the formed contacts. If the coordination number is known, the volume of liquid can be calculated using the toroidal approximation considering the boundary method. To faster develop and implement the wet granulation technology, it is necessary to be able to theoretically derive how particle size as well as consolidation influence the loading of liquid. Based on experimental work and the findings from the literature review, the Rumpf model [2] has been calibrated to predict the bulk strength in the pendular state considering an upper saturation limit of 25% for the pendular and funicular transition states (Fig. 1 a). Meanwhile, a new empirical model has been developed based on the experimental work undertaken here in order to predict the bulk strength of wet powders in the funicular and capillary states [3]. In the funicular state of saturation, an approximately linear behaviour was found with values of the bulk strength showing a small variation (Fig. 1 b).

![Figure 1. Saturation as a function of liquid content (a).](image-url)
Figure 1. Bulk strength as a function of the saturation (b)


120. SHEAR STRESSES AND OVERCOOLING AS MOVING FORCE
POLYAMID-12 CRYSTALLIZATION KINETICS

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The crystallization kinetics of polymer materials from overcooling has been investigated since 1950th [1]. Shear stresses as the crystallization kinetics parameter were considered among other things in the article [2]. The simultaneous influence of these two parameters on the crystallization kinetics of polymer materials can support PA-12 production for SLS additive technology.

In this research crystallization kinetics of polyamide-12 was investigated in dependence of two parameters: overcooling and shear stresses. The process was considered as the process with the structural reconstruction of the common system. The isothermal crystallization curves of PA-12 from overcooling and shear stresses at the temperatures 155, 160, 165°C were obtained experimentally. Based on experimental data the following parameters were determined: the induction period, nucleation and growth velocity and PA-12 conversion degree. The induction period, going before the formation of the first conversion center, allows to obtain nucleation speeds of the new structures centers, using the concrete values of the conversion degree of PA-12 from the time. The found induction period data for every moving force is an object of interest, because this values are hard to determine. An attempt to consider the combined influence of two moving forces was undertaken. The computational experiment was done using the formal analogy, suggested by the authors earlier, and Kolmogoroff-Aavraami equation [3]. The gratifying correlation between the experimental and computational crystallization kinetics curves were obtained [4].

In authors opinions, the received curves, may be useful in nozzle granulation of PA-12 melt into powder. The obtained in future spherical, given size particles will be used SLS additive technology for rapid prototyping.

Roll compaction (RC) is a widely used and cost effective dry granulation method, when moisture and heat sensitive materials are processed [1]. However, the process is time and material consuming during development and problems can occur when working with new and expensive drug substances. With the hybrid modeling of RC, it is possible to save time and material in development and scale up. The aim of this study is to examine the different compaction behaviors of microcrystalline cellulose (MCC) and lactose and to investigate the ability of the Styl'One Evolution to mimic RC.

For this study two different materials were chosen - MCC (Vivapur 102, JRS Pharma) as a plastically deforming material and lactose (Tablettose 80, Meggle) as a brittle one. Magnesium stearate (Ligamed MF-3-V, Peter Greven) was used for external lubrication on the Styl'One Evolution. The RC was performed with a Mini-Pactor (Gerteis Maschinen + Processengineering AG), the ribbon like compacts were produced with a Styl'One Evolution (Medelpharm). The hybrid modeling consists of combining a mechanical mimicking that densifies the powder the same way as on RC and a mathematical model that converts the compaction pressure into a computed specific compaction force (SCF). Two gap widths, 2 and 4 mm, and SCF in a range of 3-18 kN/cm were set. The Styl'One Evolution simulates the RC based on a modified model proposed by Peter et al. [2]. The solid fraction (SF) of the samples as a critical quality attribute was analyzed using a powder pycnometer GeoPyc 1360 (Micromeritics). The elastic recovery of the tablets was measured with a micrometer screw (Mitutoyo).

The RC of lactose resulted in ribbons with higher solid fractions (77 - 89 %) than the MCC ribbons (48 - 87 %) due to their different compaction behaviors. The compaction of lactose caused problems on both machines. Working with the Mini-Pactor powder was sticking on the rolls whereas on the Styl'One the ejection forces were so high that it was necessary to lubricate externally. It is found that the Styl'One provides results with similar curve shapes (SCF vs. SF) compared to the Mini-Pactor results but it overestimates the SF at a certain SCF for both materials. The Styl'One calculates the SF with the “in die” volume, hence elastic recovery after compression is part of the explanation for the systematical overestimation. Nevertheless, a machine specific conversion factor allows to align the Styl'One and the Mini-Pactor results.

The experiments have shown that RC hybrid modeling with the Styl'One Evolution can identify the appropriate settings to obtain ribbons with the desired SF. The mimicking gives also hints whether a material/formulation is suitable for RC. Despite these promising results, further research regarding subsequent granulation and tableting and the mimicking with complete formulations needs to be undertaken.


Pharmaceutical high shear granulation typically involves the interaction of multiple solid-phase components (active pharmaceutical ingredient, excipients) and a liquid binder. Therefore, the granulated product is characterised not only by particle size distribution but also by the distribution of individual components across the size classes. Component segregation, which can occur due to differences in the wettability of the primary particles or due to their physical de-mixing, is undesirable and its root causes need to be better understood. The dynamics of multi-component granulation can be described by population balance models (PBM), which need to be multi-dimensional if the distribution of granule composition is to be captured along with the distribution of granule size.

In this work, the batch high shear granulation process was simulated using a variant of the constant number Monte Carlo method and validated by experimental data from laboratory high shear mixer granulator. A computational parametric study was conducted to investigate the effect of primary particle wettability on the composition distribution of granules. Experiments were conducted using Avicel PH101 as the excipient, insoluble hydrophobic particles as the model active, and aqueous solution of polyvinylpyrrolidone as the binder. The granule size and composition distribution was measured by the Particle Image Analyser PartAn3D (Microtrac).
Mixing of dry or moisturized particles is a unit operation in process engineering. Usually the feed components differ in more than only one material property such as particle size, solid density and wetting properties, which in turn influence the particle mobility. For example, smaller particles can percolate through the voids of larger ones under the influence of strain and gravity. This may produce fine particle accumulation on the bottom of the mixing vessel which results in undesirable, inhomogeneous final products. When moisturized particles with different wetting properties need to be mixed, inhomogeneous agglomeration may occur as another segregation mechanism.

We present a new DEM model to study segregation in moist, cohesive mixing processes. By solving the Young Laplace equation, different particle sizes as well as different contact angles can be taken into account. Since the simplistic film model only applies to ideal wetting the particle surface is subdivided into discrete points, which allows partial wetting of the solid components. The new model also allows modelling of droplets adhering on the particles, which lead to a more realistic liquid distribution in the bulk material.
A DOWNSCALING OF THE SCHUGI FLEXOMIX AGGLOMERATOR

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The Schugi® Flexomix is a unique vertical continuous mixer and agglomerator developed to achieve a highly homogeneous mixture of powders and liquids. Liquids of varying viscosity and steam can be added using atomizing nozzles mounted to the upper part of the chamber just above the upper mixing blades [1]. Since the first design of the Flexomix in the sixties, a number of scale-ups have been implemented. These scale-ups have led to an increased feed capacity which presently stands at 40 tonnes/hour. Despite these successes recorded in upscaling, a key challenge that remains is the achievement of low feed capacities within the range 70-250 kg/hour. This difficulty is partly attributed to the lack of fully proven downscale rules and limited availability of systematic studies on the influence of process parameters on the agglomeration process for systems with low capacities.

In this study, we present findings from downscaling tests performed on two Flexomix agglomerators, the 160 litre (FX-160) and the 100 litre (FX-100). The overall goal is the development of downscale rules for these two system sizes. As first step, we investigate the effect of varying process and system parameters, namely rotation speed, pipe inner diameter, nozzle spray pattern, shaft speed and geometry of the mixing blades, on size distribution and moisture content of the final agglomerates obtained. Based on these information, downscaling rules are proposed to achieve low capacities in agglomeration systems.

125. DEM MODELING OF ADHESIVE PARTICLE MIXING

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In this study, the Discrete Element Method (DEM) is used to investigate adhesive particle mixing in a high-shear model system. The model system includes large (100 µm) carrier particles that are mixed with fine particle (5 µm) agglomerates in a Couette type mixer. The adhesion of particles due to van der Waals forces was modelled based on the Johnson, Kendall and Roberts (JKR) theory. The simulation starts with 200 uncoated carriers and 10 agglomerates with 1000 fine particles each. Simulated particles have physical properties corresponding to lactose monohydrate and D-Mannitol as common fine and carrier type particles, respectively. During the course of mixing, the agglomerates are broken, fractions adhere to the carrier particles, and there is a continuous redistribution of fine particles between carriers. The dynamic behaviour of adhesive mixing is investigated by post-processing the simulation data. The focus is to find the coated carriers and obtain information on the quality and quantity of adhered fines. Variation in the structure of fine particle agglomerates due to continuous collision and friction is studied over mixing time. Findings indicate that in the final stages of mixing, a major fraction of fine particles is dispersed evenly onto the surface of carriers, while the rest is in form of free debris. To be able to predict the degree of mixing in the system, a time-dependent index is introduced based on the standard deviation of sample compositions (Figure 1). The model also enables us to study the effect of influential parameters, such as particles surface energy and mixing power, on the characteristics of the particle mixture.

Figure 1. Evolution of standard deviation in adhesive mixing over time (a); Standard deviation while excluding debris (b).
Assessing the compaction behaviour of the primary powder in the roller compaction process is necessary to control the quality of the product. In this study, the plastic deformation of the primary particles was evaluated by determining two mechanical properties; the nano-indentation hardness and the viscoelasticity of the powder. The nano-indentation hardness of eight different materials was measured by indenting the surface of the single primary particle (Figure 1) whereas the viscoelasticity was evaluated for a powder bed using the creep test. These were linked to important ribbon properties such as ribbon strength and width in addition to the amount of fines. Rising the temperature during roller compaction process was also investigated. It was found that the plastic deformation of the material could indicate the ability of the primary powder to produce good ribbon. For the range of the investigated process parameters, the optimum hardness range that produced ribbon with good properties and small amount of fines was suggested.

Figure 1. AFM image shows indents on calcium carbonate single particle surface.
ROLLER COMPACTION OF AMORPHOUS FOOD PARTICLES

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Compaction is commonly applied in pharmaceutical and food technology for enhancing flowability, dosing accuracy as well as for reducing dustiness of powdered products. It can for example be applied to adjust the bulk density and to control reconstitution kinetics of beverage powders, leading to modified appearance or sensory profiles of the reconstituted beverages.

While roller compaction of crystalline granules is well established, processing amorphous ingredients represents specific challenges linked to their moisture sensitivity. Mechanical properties of amorphous materials gradually evolve over a wide range along the transition from the glassy to the rubbery state. This has a strong impact on the deformation behaviour in a roller compactor, the resulting granule structure and ultimately on its performance upon reconstitution. On the other hand, close moisture control also offers potential to optimize the energy utilisation of compaction processes [1, 2].

In this contribution we put a spotlight on process-structure-property relationships for compaction of amorphous food particles. We relate the physical properties of the compacted granules to initial powder properties and line settings. Final product performance characteristics like granule fragility or dissolution time are correlated to structural parameters such as density, porosity and particle size distribution, which are driven via the process and feed material properties. Mastering the product structure allows predicting its functionality.

The world of food powders constantly evolves with new compositions, new functional ingredients and new textures. The conclusion of this work is that roller compaction can help to create new interesting features for beverage powders.


Micromechanical models for the compaction behaviour of powders require knowledge of the compressive and tensile stresses transmitted between particles in contact during compaction. Contact strength also determines the strength of powder compacts.

The main objective of this work is to relate contact strength to compact strength. This is achieved in two stages: 1) the link contact strength and constitutive parameters in compaction models, which is the focus of this presentation and 2) the link between constitutive models and compact strength which is detailed in the associated poster.
This work presents tensile and compressive strength data for powder compacts. A range of commonly used pharmaceutical excipients compacted to different densities were characterised. The main objective of this work is to relate compact strength to the strength of contacts between particles, which develop and evolve during the compaction process. Such relationships have practical applications for estimating constitutive parameters for the shear and compressive behaviour of powder during compaction and breakage of tables, e.g. compaction and strength modelling.
**130. EFFECT OF KOLLIPHOR HS 15 AND SOME GRANULATING AGENTS ON THE PHYSICAL AND DISSOLUTION PROPERTIES OF MEBENDAZOLE GRANULES AND TABLETS**

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Mebendazole, a benzimidazole anthelminthic, is a drug with poor aqueous solubility. Various attempts aimed at improving the solubility of mebendazole and its release from various dosage forms have been made and reported.

The aim of the study was to evaluate the effect of Kolliphor HS 15, a non-ionic solubilizer and emulsifier on the micromeritic and dissolution properties of mebendazole from granules and compressed tablets.

Kolliphor HS 15 was employed at four concentration levels of 0, 50, 75 and 100 mg. Two sets of four batches of mebendazole were prepared by the wet massing method with maize starch (MS) and polyvinylpyrrolidone (PVP) as granulating agents respectively. Granule and tablet properties evaluated as a function of Kolliphor HS 15 concentrations were; loose densities, flow indices (flow rate, angle of repose, compress index and Hausner’s quotient, bulkiness, porosity), hardness, friability, disintegration and dissolution profiles. Two commercial brands of mebendazole employed were employed as basis of comparison.

The loose densities (bulk and tapped), haunder’s quotient, angle of repose and bulkiness were not significantly affected by variation in the concentration of Kolliphor HS 15. In granules granulated with maize starch, the hopper flow rate increased with increase in Kolliphor HS 15 concentration while the effect on tablets granulated with PVP did not follow any regular trend. There was a general decrease in the hardness of the tablets at Kolliphor HS 15 concentration of 75 mg and the friability of all the tablet batches were less than 1.0%. Kolliphor HS 15 enhanced the in vitro dissolution of mebendazole tablets in a concentration dependant manner, a behaviour which was superior to the two commercial brands of mebendazole.
Tabletting is a process in which there is high pressure compaction of the powder in the die. During compaction, the internal structure of the material changes dramatically. The initial stage is often associated with rearrangement of the particles. An important role here is played by the friction between the particles and the friction between particles and die. Subsequently, the particles are deformed and new coherent bonds are created. During compaction, the heat generated as a result of the irreversible dissipation mechanisms of the particles in contact with each other and the particles in contact with the surface of the die also plays an important role. In the case of pharmaceutical powders, this may result in degradation of the API. For this reason, it is necessary to systematically examine the powder compaction process not only from a mechanical point of view but also from a thermal viewpoint. For the past decade, the pharmaceutical industry has invested enormous efforts in Research and Development (R&D) for continuous production. In cooperation with the Food and Drug Administration (FDA) very efficient and sophisticated on-line PAT methods are being developed to control product quality in order to reduce costs and increase efficiency. Therefore, it is more than necessary to develop methods to control the properties (such as stress, density, temperature) of the material during the process.

So far a significant effect of process parameters on the final temperature, as well as on the mechanical properties of the tablet ejected from the die, has been demonstrated. There was also developed a FEM model to predict the temperature of the powder during compaction. However, no approach has been presented that can experimentally measure the temperature development in the powder during compaction. Thus a unique measurement system was developed (Fig. 1a) by which temperature, radial stress and axial stress can be measured. In this case, the powder MCC Avicel PH 102 was compressed at a compress speed of 100 mm/s in the shape of a flat-face (FF) tablet of diameter 20 mm and thickness 8.6 mm, with the temperature after compression rising above 43°C. Subsequently the results were verified by an FE model in ABAQUS/Standard software (Fig. 1b). It can be concluded that excellent agreement between the measured and calculated data (Fig. 1c) was achieved.

Figure 1. a) Compaction equipment; b) FEM simulation; c) Verification
Three-dimensional (3D) printing is a rapidly developing area within additive manufacturing that has been broadly implemented in several industries. Recently, 3D printing has also attracted increased interest in the pharmaceutical field and ground-breaking examples of biomimetic structures (e.g. organ transplants) and drug delivery systems provide fundamental knowledge for the whole medical field [1]. However, pharmacopoeia-based drug product assessment and introduction of new manufacturing principles are heavily regulated areas and can be a showstopper for this progressive development. 3D printing for material testing and fabrication of process equipment has the advantage of being fast, inexpensive and adjustable according to the specific needs, such as incorporating interfacing for process analytical technologies (PAT). This study investigates 3D printing as a tool to design and develop geometries useful for material testing and processing of pharmaceuticals.

Examples related to powder flow characterization and particle engineering will be presented. The first example is related to the application of 3D printing for designing different funnel geometries to simulate and visualize various flow patterns of powders. Powder may flow in different patterns depending on the hopper geometry, and especially the outer angle of the lower part of the funnel has a significant contribution to the flow behaviour. This study investigates a number of funnels, designed to show different flow patterns. The flow will be simulated \textit{in silico} and tested experimentally. The funnels are designed with the same top and outlet diameter, while modifications to the outer angle of the conical part of the hopper are implemented. The flow of the powders will be monitored and analysed using different PAT tools. Furthermore, the wall friction is assessed using the Schulze ring shear tester in order to predict the flow behaviour of the powder within the 3D printed funnel. The second example is related to particle engineering and specifically, \textit{in silico} design and 3D printing of flow geometries for controlled particle formation in microfluidic geometries. Printed micromixer devices are used for high-throughput production of pharmaceutically relevant particles. Flow parameters are used to control the quality attributes of the prepared particles allowing increased control and improved reproducibility compared with manual mixing and enhanced cost-effectiveness and scalability compared other micromixers.

One of the ways how to use waste glass is the technology based on the expansion of the agglomerates made from powdered glass. The technology has long been known and patented. The basis of each patent is the milling of glass to a fine powder, adding an expansive additive, creating a compact unit (agglomerates, plate, etc...) and subsequent heat treatment. In this operation the glass particles are melted and the powder ingredient is transformed into the gas phase. The result is a product that due to the presence of a gas phase is porous. The product has excellent thermal properties and chemical resistance. Therefore it is suitable for applications in special technologies. The research was aimed at the optimization of the production technology for oval agglomerates. The agglomerate size was required to be in the interval from 2 to 10 mm. The goal is to maximize the expansion ratio of the wet agglomerates prior to placement and after expansion in the oven. Wet agglomeration on a rotating plate is a suitable operation. Granules are polydispersed with an oval shape. The strength and density of the wet agglomerates is not sufficient for quality expansion. Therefore the result of the research is a two-stage technology. The first stage consists of the extruder of a special design. Powdered glass with an expansive additive and water creates the paste which is then extruded. Its moisture ranges from 15 to 17 %. The extruder provides the consolidation of the paste and its extrusion through a die where a paste is preformed. Than the material falls into the rotating plate for agglomeration. No other liquid is added here, just the forming of an oval shape of agglomerates is carried out. They are coated with very fine milled limestone on the following disc. This layer protects the granules from sticking together during the heat processing.

Figure 1. Technology block scheme.

Figure 2. From powdered glass to thermal insulation. a) powdered glass, b) wet and coated granules before thermal expansion, c) d) e) final product with various particle sizes.
This study was aimed to transfer batch wet granulation process to continuous wet granulation processes and to prepare and evaluate the granules containing metformin hydrochloride.

Granules containing metformin hydrochloride 1000 mg were prepared using a high shear granulator (HSG) and a twin screw granulator (TSG). High shear granulation and twin screw granulation was performed under different process parameters with water as liquid binder. Granules were prepared using a high shear granulator (PCM-PMA 10, GEA Pharma Systems, Belgium) and ConsiGma™-1 (GEA process Engineering, Belgium). Granules were milled or sieved after granulation and compressed with other excipients using hydraulic tablet press (NP-RD10, Natoli Engineering Company, Inc., USA). Granules and tablets were evaluated and compared for their physical properties such as particle size distribution, friability, morphology, thermal property, tablet hardness, and in vitro release.

The granules prepared using twin screw granulation had different granule properties when compared to granules prepared from high shear granulation. Both granules had mono-modal size distribution, but the granules prepared by twin screw granulation had high friability and irregular shape than granules prepared with high shear granulation. It may be due to the low shear and short granulation time in twin screw granulation. But, there were no differences in XRD patterns of granules. Also, there were no differences between HSG and TSG in tablet hardness and in vitro release profiles of metformin hydrochloride. Traditional batch production of metformin hydrochloride was transferred successfully to continuous twin screw granulation and further case studies using active ingredients should be investigated.
EFFECT OF PROCESS PARAMETERS IN TWIN SCREW GRANULATION FOR SUSTAINED RELEASE GRANULES CONTAINING HYDROPHILIC DRUG

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This study was aimed to investigate the effect of process parameters on granule properties and to optimize sustained release granules containing hydrophilic drug using twin screw granulation.

In the screening step, effects of powder feed rate, L/S ratio and screw speed on granule size distribution, granule friability and torque were investigated. For optimization, central composite face-centered design (CCF) was used to determine the optimal process parameters (L/S ratio, powder feed rate and screw rpm) for application of sustained release granules containing hydrophilic drug in twin screw granulation. Granule size distribution was determined using sieve shaker (Octagon 200, Endecotts Ltd., UK) with a series of sieves (106, 180, 300, 500, 850, 1400, 2000 and 4750 μm). The friability of granules was determined (n = 3) using a friabilator (FAT-10, Fine scientific instrument, USA). Finally, torque was monitored during the granulation process. The process parameters of twin screw granules satisfying targeted response values were calculated by JMP statistical software (Version 10.0.0, SAS Institute, USA).

The granules prepared by twin screw granulation had bimodal distribution. L/S ratio was determined to be an important factor for twin screw granules. At low L/S ratios, granules consisted of considerable amount of fines and small fraction of oversized agglomerates. Increasing L/S ratio reduced fines and increased in oversized agglomerates. Increasing feed rate positively affected oversized granules and negatively affected fines [1]. Unlike the L/S ratio, there was only a minor change in particle size distribution with varying screw speed. With central composite face-centered design, the sustained release granules with narrow size distribution and low friability and torques were obtained. The optimal process parameters for L/S ratio, powder feed rate and screw speed were 17.5%, 17.5 kg/h, and 750 rpm, respectively. At the optimized point, predicted response were 23.33% of fine, 23.72% of oversized granule 29.29% of granule friability, and 5.85 Nm of torque.

The optimal process parameters for sustained release granules containing hydrophilic drug were calculated form response surface design. This study has identified L/S ratio as the critical process parameter for preparing sustained release granules. The process parameters for preparing sustained release granules should be optimized to obtain ideal granule properties for further studies.

INFLUENCE OF DIFFERENT TYPES OF BINDERS ON DRY GRANULES AND TABLETS

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Dry binders are important for roll compaction to improve the flowability, reduce the fines and to compensate work hardening [1]. They are also needed for direct compression of tablets to ensure an adequate tensile strength and to reduce the friability. To achieve a high drug load it is crucial to identify efficient binders, applied in the lowest amount. It is also desirable to get a better understanding on the effect of powder properties on granule and tablet properties to improve the formulation development and minimize batch variabilities.

In this study, mixtures of 67% dibasic calcium phosphate anhydrate (DI-CAFOS A150, Budenheim, Germany), 20% paracetamol (Atabay, Turkey), 3% croscarmellose sodium (JRS Pharma, Germany) and 10% MCC, HPC, PVP, XPVP and PVP PVA based binders were compacted by using a Gerteis Mini-Pactor® 250/25 (Gerteis Maschinen + Processengineering AG, Jona, Switzerland). All experiments were performed at a specific compaction force of 5 kN/cm, a gap width of 2 cm and the roll speed was set to 3 rpm. The granules were compressed to 8 mm flat-faced tablets with a weight of approximately 200 mg using a rotary die press (Pressima, IMA Kilian, Germany) set to a compaction force of 10 ± 0.3 kN. For lubrication, 0.5 % magnesium stearate (Parteck LUB MST, Merck KGaG, Germany) was added.

Fig. 1 shows the results regarding the amounts of fines for the different formulations. The most efficient binder was HPC SSL SFP (Nisso, Japan), followed by PVP PVA 64 F (BASF, Germany) and XPVP M (BASF, Germany). A logarithmic correlation between the amount of fines and the particle size can be observed (R = 0.9955 (HPC), R = 0.9996 (MCC), R = 0.9984 (PVP PVAc), R = 0.9847 (XPVP), R = 0.9117 (PVP)) within one chemical type of binder with the exception of PVP binders. Similar correlations for the mean granule size and the tensile strength of tablets were observed.

Figure 1. Correlation between the mean particle size and the amount of fines in dry granules with a) HPC, PVP PVAc, XPVP; b) MCC and PVP binders, mean ± s, n ≥ 3.

To pave the way for technology transfer and scale up of the spherical agglomeration (SA) process for dimethyl fumarate, effects of the US, European and Kawashima type baffles and 0.5, 2.0 and 10 L-sized common stirred tank were studied. It was found that the particle size distribution varied significantly. However, the size-related properties such as dissolution profile and flowability of agglomerates from the same size cut after sieving could remain unchanged. The interior structure-related properties such as particle density and mechanical property of agglomerates upon baffle change and scale up from the same size cut were decayed and the agglomerates could become denser and stronger by prolonged maturation time. To maintain the same size distribution, agglomerates from any batch could have been separated and classified by sieving and then blended back together artificially by the desired weight% of each cut.
Solid state properties can be broadly classified into molecular level, particle level and bulk level. There exists a close interrelationship between each property where any change in the molecular level can directly affect the bulk behaviour of the powder. Having the same polymorph but with different morphologies enables us to understand the particle level effects on the bulk processability. Especially in the field of pharmaceutics, an early assessment of these properties and understanding the key material attributes of an active compound would shorten the timelines of drug development. Solid form screening is a typical activity related to commercial development of drug products and streamlined evaluation of processability of the identified solid forms has potentially a huge impact on overall development time. The aim of the study is to assess the bulk powder behaviour - more specifically flowability and tabletability, of a model compound crystallised in different habits using material-sparing instruments.

The model API, 5-Aminosalicylic acid, was crystallised into two morphologies (rhombohedrals and needles). Polymorphic purity was confirmed by PXRD. Automated image analysis and scanning electron microscopy (SEM) were used to characterise particulate properties. Bulk behaviour was assessed using a small scale laboratory tablet press (Gamlen Ltd, 6 mm flat-faced pre-lubricated punch), Schulze ring shear tester (RST-XS, Dietmar Schulze, Wolfenbüttel, Germany, volume 3.5 ml, Preshear 1k Pa), and miniaturised flow rate analyser (FlowPro, 5 ml).

Crystal size, based on Circle equivalent diameter ($D_{50}$), of needles and rhombohedrals were 18.39 (n = 4180) and 50.2 microns (n=2053) respectively, while the aspect ratio of needles was 0.18 and that of rhombohedrals 0.6. As expected, needles displayed poor flowability ($ff_c = 2$; flow rate = 0.99 mg/s) but produced significantly stronger tablets (see figure below) than rhombohedrals in the pressure range 35-180 MPa. The observed differences in the bulk behaviour are discussed and compared. In conclusion, two different morphologies of same polymorphs of a model API with similar sizes displayed significantly different bulk powder behaviours.

![Figure](image)

Figure (left to right): Model API, 5-ASA; SEM images of needles & rhombohedrals; and tabletability plot.
Food powders have rarely been investigated at micro-structural level by developing specific models related to the shape and structure of agglomerate materials. Most of the food, pharmaceutical and chemical powders agglomerated in industries have irregularly shaped primary particles such as maltodextrin. Majority of the research work done previously, employed the simplified spherical model for the structural characterization of agglomerates. In this work two different models are developed; (i) real model which operates on the actual structure of agglomerate, (ii) an approximated spherical model which is based on equivalent spheres. In the latter model, the same number of primary particles with solid volume equivalent to the original particles are used for the spatial morphology of three-dimensional internal structure of maltodextrin agglomerates.

The 3D volume images obtained from X-ray microtomographic technique was processed to extract data for morphological characterization. In this regard, various 3D morphological descriptors, such as coordination number, coordination angle distribution, radial distribution of primary particles, open pore porosity and spatial distribution of internal pores were evaluated by algorithms implemented in MATLAB. The results of both models were then compared and conclusions were also drawn by correlating the results with the previous works done in this regard.

The results of the two models show noticeable differences which prove that spherical model does not provide precise results for the characterization of maltodextrin agglomerates. Therefore, real structure model is the appropriate model to study the micro-internal structure of agglomerates having complex structure and irregular shapes. As an example, an illustration is shown in Figure 1.
Horizontal high shear granulation is used for producing commodity enzyme products in a tonnes per hour scale. Finding the right process and formulation parameters for a robust process can sometimes be challenging, potentially leading to process stops and/or undesired variations or effects on product quality.

Scaling down such process for finding the most suitable process parameters can also be difficult as several process parameters, such as shovel tip speed, Froude number, fill height and so on, cannot be maintained when scaling down.

This poster shows some of the work done to facilitate scale-up by the use of simple formulation models and heuristics developed through experimentation at small scale.
Metformin hydrochloride (MFM) used first therapy of type 2 diabetes mellitus (T2DM) is required to formulate controlled-release tablet (CRT) because of high frequency of intake when it is immediate-release tablet. Although MFM commercial product such as 500 to 1000 mg/tablet is sustained-release tablet, it has low patient compliance due to large tablet size. MFM CRT using fatty acid derivatives and hydrophilic polymer as release modulator (inner and outer) is become controlled-release tablet and can be overcome its problem.

In this work, the aluminum stearate in 100% ethanol binder solution was indicated the stable dispersion property and the upper adhesion uniformity on the MFM granule surface. In addition, the combination of aluminum stearate and PEO 5M was shown the most effective sustained release effect on MFM controlled release tablet. Kinetic models was fitted to Higuchi (i.e., $r^2=0.991$) and $n$ value of kosmeyer-peppas model was between 0.45 and 0.89. Micro-CT tomography showed the erosion and swelling drug-release mechanism by aluminum stearate and PEO 5M.

Figure 1. Dissolution profiles and micro-CT tomographs of MFM-CRT with different amount of Al.st and PEO 5M. M8 ($\Diamond$, Al.st and PEO 5M), M9 (X, Al.st only) and M10 (◒, PEO 5M only).
Lacosamide (LCM) is an anticonvulsant drug. It has bitter taste so it could be decreasing patience compliance in oral administration. Eudragit E100 (E100) is pH dependent polymer that dissolves under pH 5.0. LCM microspheres with E100 prepared by Spray Dry (SD) method can mask the bad taste when administrate through oral.

In this work, LCM-E100 microspheres with ratio 3:1, 1:1, 1:3 were prepared by SD method. The surface morphology was observed by SEM and physiochemical properties were evaluated by DSC, PXRD, FT-IR and E-tongue. In vitro dissolution tests were performed using USP apparatus 2. The Sensory test of LCM-E100 microspheres was scored with the bitterness level on scales of 0-4. The results showed 1:3 ratios that have the best taste masking effect. Physical stability tests were performed during 7 days at 25 °C, 40 % RH. That is evaluated by DSC, PXRD, FT-IR, SEM, in vitro drug dissolving test. In this duration, 1:3 ratio was observed that lacosamide solid state transform amorphous into original form as crystal form and much amount of lacosamide was exposed on the surface of microsphere. That means had been decreasing the taste masking effect. So considering taste masking effect and stability that LCM:E100 1:1 formulation is the best formulation in three ratios.

SEM images and DSC thermogram of LCM-E100 1:3 microspheres after storage 7 days at 25 °C, 40 % RH.
143. OPTIMIZATION OF SHELL DRYING CONDITION FOR CO-EXTRUDED ALGINATE ENCAPSULES CONTAINING VEGETABLE OIL

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Conventional lipid-based formulations had some disadvantages such as complex manufacturing and low stability, so it is advisable to transform into solid form. This study prepares the seamless capsules of vegetable oil via co-extrusion using various concentration of alginate, and optimizes the drying parameters on its solidification.

The capsules containing vegetable oil were prepared by co-extrusion method (Encapsulator B-390, BUCHI®) with 2, 2.25, 2.5 and 2.75% alginate as outer encapsulants. In order to study the influence of drying parameters on solidification of the capsules, DoE (Design of Experiments) was performed using a two-factor three-level factorial design (3²), with ethanol concentration for rinsing and drying temperature as independent variables and encapsulation efficiency as response variable. Non-destructive characterization of the capsules, the optical microscopic images were taken by optical microscope (BX51, OLYMPUS®), and the 3D images of z-stack scan were taken by confocal laser microscope (DE/LSM710, ZEISS®). Then, these images were analyzed by Bitplane Imaris® image analysis software.

The alginate concentration and its viscosity showed a strong relationship (RSq=0.9882), and size distribution of the capsules increased as alginate concentration increased. The capsules containing 2.5% alginate revealed ideal characters that consisted a single oil component per capsule and showed quite spherical morphology. The results of DoE on solidification process showed that the prediction values were significant (p=0.0022 and RSq=0.98) and both ethanol concentration and drying temperature had significant influence on encapsulation efficiency. The surface of responses was investigated in order to find the optimum solidification parameters. The response surface indicated that 36.15°C of drying temperature and 38.2% of ethanol concentration results in the highest encapsulation efficiency.

Co-extruded alginate capsule containing vegetable oil.
Continuous twin screw wet granulation has already become a method choice for granule production in the pharmaceutical industry. It is clear from the literature that there is a need to develop the predictive models in order to improve process efficiency. Previously, population balance modelling (PBM) has been done in twin screw wet granulation using specific screw configurations involving zones of kneading and conveying elements. However, there is need to develop these models discretely as well as holistically to understand the role of different screw elements and to study the granule evolution along the barrel length. In the present study, granulation rate processes viz., nucleation, breakage, consolidation and layering, occurring along the length of the twin screw granulator were simulated discretely as well as holistically using PBM and the models so developed were validated experimentally. These models can be utilised in improving the process design and predict the process performance in the industry.
RECOMMENDATIONS FOR INDUSTRIAL AMORPHOUS FOOD POWDER AGGLOMERATION FROM A PARTICLE PERSPECTIVE

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Agglomeration is a widely used unit operation in the food industry to improve the properties of fine powders that are often composed of hygrosensitive amorphous material. Just to mention some examples of the resulting advantages for processing and also consumers: a better flowability is observed for larger particle agglomerates next to an improved dosability, easier handling and a more appealing appearance.

However, many agglomeration processes in the food industry like fluid bed agglomeration or roller compaction are by far not run at their optimum and the resulting particles are not stable enough to resist wear during packaging and transport. In contrast to this, agglomerates can also be too dense and do not dissolve quickly upon reconstitution. The output of these processes could be improved and the recirculation or waste product reduced if the interactions between the individual particles in the process is optimized.

The missing knowledge on the way individual amorphous particles behave under certain agglomeration conditions like humidity, temperature, pressure, contact time and deformation can be experimentally accessed via Micromanipulation and Atomic force microscopy.

Based on the results from cohesion studies of amorphous model food particles using these tools, recommendations are given for process parameters in industrial applications such as coffee agglomeration.

Operational windows for optimum particle cohesion can be quite restricted when it comes to temperature and humidity. It could be shown that for amorphous hygrosensitive materials, these are however key parameters determining if agglomeration takes place or not and even if blockage of an agglomeration equipment can occur due to a collapse of the particle structure.

As a next step following this study, real life food materials composed of amorphous substances should be tested and the recommendation based on the model material behaviour verified.
INVESTIGATION INTO MECHANISM OF GROWTH BEHAVIOUR OF A NON-WETTING SYSTEM

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Wet granulation is a size enlargement process, commonly found in food, fertilizer, pharmaceutical and detergent industries. Granulation of non-wetting powder is a common problem in the pharmaceutical industry, which compromises a uniform distribution of drugs in the granulation batch. The effects of hydrophobic powder in wet granulation has been investigated by some studies, including observing the formation and stability of liquid marbles, liquid marbles morphology, examining the driving force of liquid marbles formation, and looking at hydrophobic powder distribution for different ranges of formulation wettability. The granulation growth behaviour of pure hydrophilic powder is becoming established but an understanding of the effect of heterogeneous-wetting components on the granule growth mechanism in high shear granulation remains relatively unknown, and this forms the motivation of this study.

In this study, the effect of hydrophobicity, impact velocity and liquid viscosity on granule structure and size is investigated. Mixtures of hydrophilic and hydrophobic glass beads were granulated with PEG solutions in a tumbling drum. The results show that granule size increased with an increasing binder viscosity, and decreasing tumbling speed and contact angle. Hollow granules were obtained with high binder viscosity, and the occurrence of granule coalescence was increased at high binder viscosity. Further experiments will evaluate the effect of binder viscosity and particle properties on granulation behaviour inside a high shear granulator.
In wet granulation process, liquid binder is used to encourage the particles to stick to each other and produce agglomerates. High shear mixer is commonly used equipment in which the powder and the liquid are agitated by rotating impeller. Due to the intense mixing, the particles are continuously driven towards the granulator wall. If the particles are sufficiently wetted or plastificated, it could adhere to the wall as a monolayer and there is a potential for more particles to build up over the initial layer. The macroscopic scale of this process is known as caking or unwanted granulation. The caking exhibit significant importance in industry as it negatively affects the quality and the yield of the granulated material.

The present study investigates the build-up of caking layer during wet granulation process. The experimental setup is consisted of vertical laboratory scale mixer and high speed camera. The amount of deposited material and particle velocity were determined from the acquired images by particle image velocimetry (PIV). The caking behaviour was investigated in rotational speed range that is covering both ‘bumpy’ and ‘roping’ flow regimes. Inert poly methyl methacrylate (PMMA) plastic beads are used as a model particles and maltodextrin solution is used as a binder. The binder viscosity was varied by changing the amount of maltodextrin in the solution. The surface tension was also changed by addition of sodium dodecyl sulphate (SDS) as surfactant. The high speed monitoring showed that the caking layer forms at the bottom of granulator bowl and rises up horizontally over the perimeter towards the rim. The build-up time is dependent on the liquid distribution in the agitated particle bed. Increasing the binder viscosity leads to significantly slower liquid distribution and thus delaying the caking build-up time. Through the high speed camera monitoring the mechanism of the particle wall deposition during wet granulation was visualized.
INVESTIGATION OF THE PRODUCTION OF WET AGGLOMERATES OF DURUM WHEAT SEMOLINA USING A FLUIDIZED BED GRANULATOR

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Mastering the industrial processes in which wheat powders are used to produce couscous is still partly based on practical industrial experience and empirical knowledge. Wet agglomeration, rolling, cooking, drying and screening are the main unit operations which are sequentially involved in the couscous grain production. Granulation is the main step that determines the production yield and the final size and shape of the couscous grain. Control of granule size distribution after the wet granulation stage is a very important quality constraint. The objective of this work is to explore whether the novel technique of fluidised bed granulation can produce agglomerates of durum wheat semolina and to investigate if this method could prove a successful alternative to the conventional method using low shear mixer technology to produce the couscous grains.

The couscous agglomerates were produced in a batch fluidised bed granulator with water as the binding medium (top spray). The size, shape, hydrotexural properties (moisture content and compactness) and strength of the granules were measured. Fluidised bed granulation provided a more controlled size distribution than is achievable with the corresponding low shear granulation approach. The agglomerates have specific hydrotexural properties, with different values of their functional attributes that allow us to think to a new ways of texturing durum wheat semolina agglomerates. The final grains size, shape and moisture content were similar to the values measured for commercially available samples. Nevertheless granule compactness was lower. The strength of the granules increased with an increase in the size and the compactness of the final couscous grain.
Oral bioavailability of drug depends on its solubility and/or dissolution rate, and dissolution may be the rate determining step for the onset of therapeutic activity. Poorly aqueous soluble drugs are usually characterized by low bioavailability due to low absorption. The effects of varying concentrations of polyethylene glycol 4000 (PEG 4000) and pH of dissolution medium on the in vitro release of theophylline embedded in a poly (acrylic) acid polymer, Carbopol 940 (CP940) and in a plastic matrix, ethyl cellulose (EC) were investigated. Theophylline granules and tablets containing the polymer matrices and surfactant (PEG 4000) were prepared by the conventional wet granulation method. Mechanical properties of tablets were determined using standard methods, while the dissolution profiles of the tablets were assessed in three dissolution media, (0.1N HCl), simulated gastric fluid, SGF, and simulated intestinal fluid SIF using the BP paddle method. The release of theophylline from CP940 matrix was generally faster in SIF and in SGF than in 0.1N HCl. The presence of PEG 4000 in the EC matrix led to marked retardation in theophylline release while enhancement in theophylline release occurred from the CP940 matrix. The release mechanism of theophylline from the matrices ranged from diffusion to non fickian transport.
In twin screw granulation process, the factors affecting products attributes have been studied in-depth. During this investigation process, the importance of fill level came into sight. Fill level referred to the amount of material in the barrel of twin screw granulator. It could affect the compaction between system and material and influence the granule attributes including size, strength, etc. The variation of fill level occurs when varying the screw speed or configurations and distorts the results. However, regarding about how to eliminate its impact, insufficient researches has mentioned.

In this paper, the powder feed rate was varied based on the screw speed or configurations, in order to maintain the mass of material in the barrel (fill level). In such cases, granules were collected and its attributes including size, strength, morphology has been analysed. It reveal the effect of screw speed or configuration on the granule attribute in a fixed fill level. In addition, due to the addition of tracer in granulation liquid, the colour distribution in granules could be seen as an indicator of binder dispersion. Therefore, the absorbance of the solution from the granule in difference size ranges was obtained, in order to clarify the binder dispersion in different speed or configurations. The relationship between binder dispersion and granule size in different screw speeds or configurations could be acknowledged.
A catalyst support is often used to disperse a catalyst material to enhance the contact area for reaction. This catalyst support in catalytic converters is in the form of a washcoat layer. Given the role of the washcoat layer in catalytic converters, its mechanical strength is of extreme importance as it determines the service life of catalytic converters.

In reality, washcoat layers are found to fail in both a cohesive and an adhesive mode. However, in the literature, there are currently limited publications that present a method capable of quantifying the cohesive strength of washcoat layer. One of these limited publications introduced a cohesive strength quantification technique in which a washcoat was made into a tablet and the tensile strength of the tablet measured as the cohesive strength of the washcoat layer [1]. Despite the novelty, there were still problems with the method suggested as tablet splitting occurred at low pHs due to a non-uniform drying system.

In the current paper, a more uniform drying system was suggested, which lead to the formation of intact tablets at low pHs. The cohesive strength of the washcoat layer was then successfully determined at these pHs.

The washcoat layer was prepared by drying a suspension of ceramic particles of known size followed by calcination. The pH of the suspension was adjusted and the drying conditions were also controlled. The strength results obtained were correlated with the motion of washcoat particles during drying to explain the various patterns of particle packing found at different preparation conditions.

Encapsulation and controlled release of active agents is a common practice in many industrial fields to improve the processing as well as the properties of materials and final products. Today, a large variety of chemical admixtures are used in construction materials, the performance of which could be improved by a better dosage control. This research presents selected investigations of a comprehensive study encapsulating dry superplasticizers in matrix based encapsulation systems using high shear agglomeration. As basic material commercially available fly ash, which is commonly applied as supplementary cementitious material in the field of construction materials, was granulated by high shear agglomeration to produce matrix based encapsulations.

The statistical evaluation of the determined data indicates that the particle characteristics of the agglomerates like the median particle size $d_{50}$, the scattering parameter as well as the production were mostly influenced by the binder viscosity during the investigations. The delayed admixture release was enhanced by high binder viscosity and low energy input during the agglomeration process due to a coating of the bigger superplasticizer particles by the smaller fly ash.

The obtained results confirm a theoretical model of encapsulation and admixture release, which was derived from pharmaceutical drug release concepts and adapted to construction materials. The results indicate that the matrix based encapsulation is a promising technique for future applications in the field of construction materials.
Single particle motion in a two-dimensional granular system is investigated in the time range from ballistic to diffusive. The system consists of 1 mm stainless balls on a plane circular surface. The motion of the particles is produced by an alternating magnetic field applied perpendicular to the surface of the container. The mean square displacement of the particles is measured for a range of low concentrations. It is found that increasing the concentration of particles maintaining all other conditions constant is equivalent to do a zoom out in both the spatial and temporal dimensions and in this way one can access the full range from ballistic to diffusive motion and to obtain details of the motion at different instances. A comparison with the solution of the Langevin equation for the mean square displacement of a single particle in a thermal bath shows an excellent agreement for the full time range.
Poor aqueous solubility of active pharmaceutical ingredients (APIs) is a common problem in pharmaceutical development. Wetting is the first and the most important step for a solid drug to dissolve. Amorphous solid dispersions provide a promising possibility of improving the dissolution rate of poorly water-soluble drugs and thereby their absorption. The solid dispersions can be defined as a dispersion of one or more APIs in an inert carrier in the solid state. Typically, APIs are molecularly dispersed into the hydrophilic polymeric carriers which enhance aqueous solubility and oral bioavailability. The solid dispersions can be prepared by three different ways, melting, solvent method or melting-solvent method. However, due to the higher energy of the amorphous form of drug, amorphous dispersions are thermodynamically unstable and may crystallize. The crystallization often starts at the surface of amorphous materials and it is preceded and induced by the structural relaxation of the surface. The structural relaxation at the surface is faster than that within a solid body bulk and it might be defined as a loss of energy of the fresh amorphous material during aging.

In this work, the solid dispersions and corresponding physical mixtures containing acetaminophen or ibuprofen and one of the three polymers (Kollidon® 12 PF, Kollidon® VA 64 or Soluplus®) were studied in different weight ratios. The solid dispersions were prepared by melt method and the inverse gas chromatography (IGC) was used to characterize the surface energy of the prepared sample. The advantage of IGC is measurement of surface adsorption monolayer coverage because this first adsorbing layer influences process such as wetting. IGC is also a suitable technique to detection of the surface structural relaxation. The measurement was performed at infinite dilution when very small concentration of probe vapours were injected so the probes preferentially interacted with the highest energy sites on the surface of the sample. A series measurements with different gas phase probes were used to characterize the surface energy. Furthermore, the rate of release APIs from the solid dispersions and physical mixtures were evaluated by dissolution in the flow-through cell apparatus.

The results showed the differences in the drop of the surface energy. The dispersive component of the surface energy significantly decreased with increasing polymer content. The drop was nearly linear for the physical mixtures containing acetaminophen and Kollidon® 12 PF or Kollidon® VA 64. In contrast, the solid dispersions showed a significant reduction in the dispersive component of the surface energy than the corresponding physical mixtures. For both solid dispersions and physical mixtures, containing acetaminophen and Soluplus®, the progress of the decrease of the surface energy had the same trend. In contrast, several phenomena occurred during the measurement of the surface properties of solid dispersions and physical mixtures containing ibuprofen. The surface structural relaxation was one of them and still-rising retention time of nonane was the indicator. The dissolution testing revealed the influence of the surface energy during dissolution. The lower values of surface energy were correlated to improve dissolution.
Caking of powders during processing and storage is a ubiquitous problem in many industries, which could significantly decrease products quality and lead to economic losses. It is hence important to know the conditions under which powders caking occurs. In this study, the caking behaviour of three powder materials (PVP, HPC and Mannitol) has been investigated. The ball indentation method (Hassanpour and Ghadiri, 2007) is used to assess surface caking effected by relative humidity (RH), temperature and time. The resistance to powder flow, as indicated by hardness is measured by the ball indenting the powder bed surface. For powders prone to caking, the surface hardness increases with increasing RH and temperature. Moreover, high temperatures could significantly accelerate the caking rate of powders. Irreversible caking occurs in PVP and HPC at 75% RH. However, the caking of mannitol is reversible. To examine the caking mechanism of PVP and HPC, critical glass transition RH was determined for PVP and HPC at 25 °C and 45°C. The values are 63% and 53% for PVP and 61% and 50% RH for HPC, respectively. When PVP and HPC are exposure to 75% RH, they are transformed from a glassy state into a rubbery state, and the particles coalesce and the volumes of powder beds are significantly reduced. The moisture contents at which the glass transition occurred for these powders is comparable with the critical moisture contents predicted by the dynamic vapour sorption measurement. The results show that ball indentation method could be a fast and effective method for assessment of powder surface caking.

Powder granulation in different industrial processes are carried out to improve the handling and storage behaviour of solid materials, however on the other hand, uncontrolled auto-agglomeration of powders may occur due to mechanical vibrations as it goes through the process, leading to undesired problems. Auto-agglomeration is often referred as a binderless granulation process that produces granules with an inherent strength. The scale and behaviour of these agglomerates depend on the inter-particle attractive forces along with particle properties. Therefore, it is important to understand inter-particle interactions which result in the formation of agglomerates. In this study, the process of agglomerate formation is examined. The materials used for this investigation are titania, alumina and two API’s powder which are mechanically vibrated under controlled conditions to induce clustering and promote auto-agglomeration. The experimental results enhance the current understanding and give an insight on mechanism of auto-agglomeration upon vibration in materials having different physical and chemical properties.
EFFECT OF PARTICLE SHAPE ON THE PACKING AND FLOW BEHAVIOUR OF GRANULAR MATERIALS

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Particle shape is one of the most important properties of particles, and it affects the packing and flow structures that are critical to transport properties such as permeability related to pore connection and thermal conductivity related to particle connection. Particle shape can be regular or irregular. To be more quantitative, recent studies are focused on particles of well-defined shapes. In particular, ellipsoids attract a lot of attention in recent years as they can represent a large number of shapes, e.g. from platy to elongated. In this paper, we give a summary of studies of ellipsoidal particles on the basis of discrete element method, and examine the effects of particle shapes in some typical particulate systems, including: (1) particle packing, focusing on how aspect ratio affects packing density and structure for coarse and fine ellipsoids [1,2]; (2) sandpile formation, focusing on how aspect ratio affects the angle of repose and stress dip distribution [3]; (3) fluidization, illustrating how particle shape affects the bed permeability, orientation, and bed flow/force structures [4,5]; and (4) hopper flow, demonstrating the dependence of discharging rate of hopper flow on particle shapes [6]. The results show that discrete element method for ellipsoids provides a useful approach to investigate shape effect on the behavior of granular materials with shapes varying in a large range.


Granulation is a key step in manufacturing of solid oral dosage formulations within the pharmaceutical industry as it is used to improve material flowability and content uniformity. Granulation is achieved by either dry or wet modes; dry granulation is used for the continuous production of granules without the requirement of a drying stage, where it is a suitable method for heat and moisture sensitive materials. Roller compaction is the primary process for dry granulation, as powders are first compacted to form larger particles or granules [1]. Through the development of a process map, a correlation can be made between the input variables, such as roll pressure, roll speed, screw speed and granule properties such as porosity/density. This method reduces development time, quantity of materials, and cost. It should be noted that these process maps are limited to the specific type of formulation and equipment used in the experimental design. In this study, a variety of formulations are investigated to identify process/ granule property relationships and to determine critical quality attributes. Microcrystalline cellulose (MCC) PH 102 and lactose monohydrate are used as model API materials with 1 wt.% magnesium stearate (MgSt) as lubricant. A top-fed roller compactor “Freund TF-MINI model” is utilised in conjunction with process analytical tools (PAT) such as near infrared (NIR) spectroscopy and a Geopyc 1360 envelope density analyser to measure the granule porosity/density [2].


Traditional pharmaceutical processes comprise of a series of batch-wise operations. Nowadays, a shift is being made from these batch processes to continuous manufacturing, to cope with the inefficiencies and high cost involved in process development. Twin-screw wet granulation is an up- and-coming continuous granulation process that is being assessed for its performance in the solid dosage manufacturing. However, since these continuous processes are fairly new in the pharmaceutical industry, detailed process knowledge and understanding is still lacking. Application of mechanistic models can help in bridging this gap by assessing the experimental data and uncovering the underlying mechanisms. In this work, a Population Balance Model (PBM) is developed for predicting the granule size distribution inside the granulator starting from the pre-blend, up until the wet granules at the end of the process. In PBM, physical processes like aggregation and breakage of granules are represented by kernels which are often empirical in nature with fitting parameters. Model equations are solved using the Cell Averaging Technique (CAT) which is able to deal with aggregation and breakage. Different aggregation and breakage mechanisms can be implemented using different kernels. However, models are only useful when calibrated/validated using experimental data. Calibration of a PBM presents unique challenges in various intermediate steps.

First, the model grid needs to be defined (i.e. number and location of size classes). Different measurement techniques (laser diffraction, QICPIC, sieve analysis) use different grids. As each measurement technique has its own peculiarities, it is difficult to compare measurements performed with different techniques. Second, an objective function needs to be defined. The current practice to calibrate PBM is similar to how this was done for time series and using deterministic models. Sum of Squared Errors (SSE) and Root Mean Squared Error (RMSE) are thus typical gold standards. Similarly, the information of a whole particle size distribution can be condensed into some characteristic numbers, such as mode, mean, span, and the Sauter diameter. Proper evaluation is needed to confirm whether this is indeed the way to go to obtain a good modelling practise for PBM. A lot of freedom is available when dealing with particle size distribution, but the question is how to deal with this kind of freedom and how it is best coupled to the modelling objective. Third, a technique to find the minimal value of the objective function has to be selected. In this study, predictions of a selected PBM formulation are generated using a global parameter space exploration by means of a large set of Monte Carlo simulations. Changing the aggregation and breakage kernel parameters yields different size distributions. Different objective functions are evaluated to determine the objective function whose optimum yields the optimal agreement between the simulated and measured particles bearing in mind the objective. This optimal agreement, within a predefined error range, is called the calibrated model for that process setting. This study is repeated for different process settings of the twin-screw granulator. By comparing the calibrated results for different process settings, the aggregation and breakage mechanisms can be identified, and the most dominant regimes can be found. Guidance on the different choices to be made during the calibration process will be provided.
Die filling is an essential step in the manufacturing of particulate products in the fields such as metallurgy and pharmaceuticals. An accurate prediction of the quantity of powders deposited into the die has so far not been achieved. In this work, the mass flow rate and the deposition time for a wide range of powders were measured experimentally using a custom-made die filling system instrumented with a dynamic pressure sensor. The length of the shoe was varied in order to explore its impact on the deposition time. The deposition of powders into an open beaker and an air tight die was also examined. The mass flow rate was found to be significantly reduced during the deposition of the powder into the air tight die. This is due to the effect of the air present in the die, as the air inside the die could only escape by permeating through the powder bulk in the shoe. A semi-empirical model based upon the modified Beverloo equation was also developed. The model was validated using the experimental data. It was shown that the model could well predict the die filling characteristics of a powder, including the critical filling speed, the final powder mass deposited into the die and the mass flow rate.
Roller compaction is a dry granulation technique used in many industries especially the food and pharmaceutical industries. During the roller compaction, not only the properties of the primary powder will affect the product quality, but also the process parameters. A change in the process parameters during roller compaction results in ribbon of different properties. In this study, an online thermal imaging camera was used to measure the temperature of ribbon during production, which was used to explain the difference in ribbon properties at various process parameters.

Lactose powder was used as primary powder and ribbons were produced at different process parameters. The temperature of the ribbon during production was found to increase with increasing both the gap between the two rollers and the roller speed. Increasing the gap and the roller speed increases the speed of the feeder screw in order to deliver more material and fill the set gap. This resulted in higher accumulation of heat inside the powder and increased the temperature of the produced ribbon. Increasing the roller gap during production resulted in wider ribbon and decreased the percentage of fines in the product. This was a signature of better powder distribution across the roller width. It was found that increasing the roller gap during the roller compaction decreased the width of the ribbon, which consequently increased the fine percentage in the product. The feeder screw speed was found to have a similar effect as the roller gap since the increase in the gap during the roller compaction increases the feeder screw speed due to the use of the automatic feedback system.
Many functional materials exist which exhibit excellent properties for various sustainable processes such as catalysis, removal of pollutants and recovery of valuables. However, most of these materials are only available in the powder form limiting their use and large scale application.

The focus of our current research is on the shaping of this functional inorganic materials into microspheres with controlled shape and porosity using vibrational droplet coagulation.[1] The technology allows the formation of very uniform microspheres with a high sphericity and controlled hierarchical pore distribution. This technology starts from a suspension containing the active powder material, solvent and binder system. This suspension is pushed through a nozzle obtaining a laminar flow. This flow is broken into uniform droplets by the application a controlled vibration. The droplets are then solidified through ionotropc gelation when biopolymers are used as binder or through sol-gel chemistry.

These efforts lead to uniform spherical microspheres with a narrow size range, tunable between 50 and 3000 µm. They have the benefit of controlled porosity, low mass transfer limitations and low pressure drop. The structural, surface, textural and optical properties of the microspheres were thoroughly investigated using XRD, FTIR, N₂ sorption, optical and FESEM microscopy techniques.

Figure 1. Experimental setup of the process (left) and Al₂O₃ spheres (left) produced with it.

This work deals with numerical simulation of powder caking process caused by capillary condensation phenomenon. Caking consists in unwanted agglomeration of powder particles. This process is often irreversible and not easy to predict. To reproduce mechanism involved by caking phenomenon we have used the Discrete Elements Method (DEM). In the present work, we mainly focus on the role of capillary condensation and subsequent liquid bridge formation within a granular medium exposed to fluctuations of ambient relative humidity. Such bridges cause an attractive force between particles, leading to the formation of a cake with intrinsic physicochemical and mechanical properties. By considering a Representative Elementary Volume (REV), the DEM is then performed by means of a MULTICOR3D software taking into account the properties of the cake (degree of saturation) in order to establish relationships between the microscopic parameters and the macroscopic behaviour (tensile strength).
Caking refers to undesired agglomeration of powders and could result to severe problems during the storage and handling of powders. Although the caking of powders has long been studied in literature, this process has not yet been fully elucidated. Indeed, the caking is a complex and multi-variable process which bring into play a multitude of different mechanisms based on the environmental conditions and the chemical nature of materials. According to literature, the most impacting parameter on the caking is the relative humidity of the ambient atmosphere. So far the majority of investigations on this topic have focused on the role of relative humidity above the Critical (Deliquescence) Relative Humidity (DRH) for hygroscopic materials. The role of RH on the glass transition temperature ($T_g$) lowering of amorphous powders has also been subject of a broad investigation. However, the relative humidity could also result in caking of non hygroscopic crystalline materials through its effect on the phase transition of those materials. An important example of this kind of material is anhydrous lactose which can undergo caking when exposed to a high relative humidity so that a crystalline phase transition to lactose monohydrate could occur.

This study deals with the caking behaviour of anhydrous lactose at controlled relative humidity and pressures. The experiments were conducted on a home-made multi-cell caking device situated at controlled temperature and relative humidity. The results point clearly out the appearance of caking phenomenon due to lactose anhydrous to monohydrate phase transition. The effect of operating conditions (RH, normal pressure and time) on the caking extent and the structural properties of resulting cakes was then investigated. The results were interpreted based on intrinsic kinetics of phase transition established at different RH using a SPS instrument allowing the measurement of water vapour sorption of samples.
A STUDY OF ADHESIVE FORCES BETWEEN MODEL DETERGENT PARTICLES TOWARDS CAKING PREDICTION

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Powder caking, being an undesired effect of particles to bond, form clumps and hinder independent movement, is commonly encountered in chemical, pharmaceutical, food and detergent industries both during production and storage. Caking studies have been mainly focused on bulk materials, of which an overview was presented by Calvert et al. [1]. To enable a more fundamental understanding and prediction of caking, studies both on bulk materials and on individual particles are required [2]. As a first step towards understanding of caking mechanisms, a study of interactions between model particles representative for detergents will be presented here.

Adhesive forces between a pair of particles of the same composition for different chemistries were measured using a micromanipulation setup very similar to the one presented by Zhang et al. [3]. Particles were prepared by coating microcrystalline cellulose spheres of narrow particle size distribution (PSD) with a thin layer of one of the detergent chemicals in a fluidized bed. Coating onto these spheres was done to minimize effects of particle size and shape on the measurement of adhesive forces. During micromanipulation experiments, particles were slightly compressed and subsequently retracted to measure the maximum pull off force using a force transducer in the µN-range. Typical obtained forces were in the range of tens of micro-Newton and allowed for making a quantitative ranking of chemicals believed to cause the highest adhesive forces at usual lab conditions. These results can be used for product design regarding caking prevention on one hand, and on the other hand for modelling of adhesive forces at particle level to predict caking at bulk level. Future work will include control of relative humidity and temperature during measurement to investigate the effects of these two environmental parameters on the results. The effect of liquid bridges between two particles will be studied as well.

This study being part of the 'CHARIOT'-project, we are grateful for AMSCI funding.


Granules represent an intermediate stage between the primary particles (active pharmaceutical ingredient - API, excipients) and the final solid dosage form (tablet, capsule filled with granulate). It is still an open question to what extent the variability in the dissolution rate of individual granules affects the overall release rate of the active ingredient from the final product. Upon closer inspection, the bulk dissolution properties of granulate can be regarded as the sum of the contributions of individual granule size fractions and even individual granules within each size fraction. In pharmaceutical granulation, the composition (API/excipient ratio) and internal structure (porosity, pore size distribution, relative particle arrangement) of individual granules can be far from uniform. By a detailed analysis of a statistical sample of single granules from each size fraction we can reach a better understanding of the underlying dissolution mechanisms of the bulk granulate and also the final dosage form. The structure of the granule, its hardness and its size all jointly influence the mechanism of API liberation.

Our approach is the combination of UV imaging of single granule dissolution with its structural analysis (micro CT and SEM). Combining these characterisation methods allows us to study the factors controlling the rate of the dissolution such as internal mass transfer, external mass transfer, or true dissolution kinetics of pure components. In the case of external mass transfer limitations, the key parameter influencing the dissolution kinetics is the concentration gradient between the API dissolved on the granule surface and in the bulk of the dissolution medium. This gradient can be visualised by UV imaging of a single granule. The main advantage of this method is the possibility of chemical identification of the API, thanks to the fact that the majority of APIs absorb in the UV range, thus separating the dissolution of the API from dissolution of the excipients. Short acquisition time also allows us the measurement of the granules with fast disintegration and API liberation. Using dissolution media pre-saturated with one of the formulation components, combining the results from UV imaging with the structural information obtained using micro CT and with the characteristics of mechanical properties using texture analysis, we can obtain helpful information leading to a higher level of process understanding. The single granule dissolution experiments will also be combined with a microstructure-based model of granule dissolution developed in our group.
Granulation is the process of forming large aggregates from fine particles using a granulation device. Granulation is used in several industries from pharmaceuticals to chemical and fertilizer production. The process starts when the binder particles and primary powder particles interact to form new entities called nuclei. On further interaction with other particles in the systems granules are formed. This research will study the effect of four process variables: speed of mixer rotation in the range 100 to 200rpm, powder bed mass (25 to 40g), mass of the initial granule (0.6 to 2g), and binder viscosity (water, CMC solutions with concentrations in the range 0.5 to 20g/L) on single nuclei growth kinetics in low mixing devices. The powders under study are: lactose, tea, sugar, starch, and limestone. The results show the initial size of nuclei, the initial mass of the powder bed and binder viscosity and speed of rotation all influence the rate of nuclei growth and this final size of nuclei.

Figure 1. Effect of binder viscosity and rotational speed mass uptake by the nuclei.
The overall purpose of this research paper is to study the effect of vessel shape and speed of rotation on the mixing process of a binary system of solid particles. Discrete Element Modelling (DEM) was used to study the mixing of a completely segregated mixture of limestone and sugar particles in five different 4-bladed vessels of the same volume: a 30° angled vessel, a 45° angled vessel, a round-edged vessel, a cylindrical vessel, and a parabolic vessel. Three simulations were done for each vessel type varying the rotational speed of the blades from 150 rpm to 300rpm to 400rpm. The mixing index and the rate of mixing were calculated for each experiment and it was observed that mixing is highest for all vessels when the rotational speed is 150 rpm whereas the rate of mixing is highest at the middle speed of 300 rpm. Analysing the effect of vessel shape on mixing shows that mixing is most efficient in a round-edged vessel while the rate of mixing is highest in a cylindrical vessel.

Figure 1. Effect of impeller speed and mixer geometry on mixing index.
In wet granulation process using fluidized bed granulator (FBG), when spraying hot binder solution, the evaporation rate of water in the binder droplets contacting with particles/granules will vary. The change of temperature of the particles with time is related to both the wetting stage where the hot binder comes in contact with the particle and to the evaporation of the water when the binder contacts with the air. In this study a CFD-DEM model was used to relate the change in temperature of the particles/granules to a predominant mechanism (wetting or evaporation).

Online thermal imaging technique is adopted to monitor the change in temperature of particles/granules with different size. This technique is coupled with the proposed simulation model to ensure its validity. The proposed CFD-DEM model will be adjusted and implemented into the software to have more comprehensive data to prove the method developed in this research.
Lactose and Mannitol are some of the most commonly used powders in the pharmaceutical industry. The research published so far highlighted the effects of process and formulation parameters on the properties of the granules and the tablets produced using these two types of powders separately. However, the comparison of the performance of these two types of powders during twin screw granulation has received no attention. The present research is focused on understanding the granulation mechanism of two types of pharmaceutical powders with varying properties (primary particle size, structure, flowability and compressibility). Three grades each of lactose (Pharmatose 450M, Pharmatose 350M and Pharmatose 200M) and mannitol (Pearlitol 50C, Pearlitol 200SD and Pearlitol 300DC) were granulated at varying liquid to solid ratio (L/S) and screw speed. It was found that properties of powder play significant role in determining the granule size, surface and structure.
The presence of liquids has a significant effect on the dynamics of granular flow. Using a combination of experimental study and discrete particle method simulations (DEM), we investigate the effects of capillary force, liquid viscosity and particle size on wet granular flows, and we establish a methodology that ensures the control of the bed flow motion in a rotating drum.

The velocity profile of the particles in the rotating drum is determined using particle tracking method and compared to the DEM simulation results. Capillary and viscous forces are included in the DEM model to describe the interactions between surface-wetted particles.

We show that the strength of capillary force between two adjacent particles can be altered through surface properties modification of the glass beads, thus, under the right conditions; we demonstrate that the bed flow motion can be controlled. Liquid viscosity effect on the bed flow motion is also investigated under low capillary forces. The capillary force between the particles is significantly reduced by making the glass beads hydrophobic via silanization. The simulation and experiment results were comparable in terms of the flow patterns and dynamic angle of repose. We find that liquid-induced cohesion increases the width of the flowing layer and the dynamic angle of repose. However, it decreases the particle flow velocity in the drum. We were able to obtain similar bed flow motion for different particle sizes, and the flow control methodology is found to be robust in the studied flowing regimes.

Flow motion and velocity gradient of the bed in the rotating drum at 25 rpm. a) and b): experiments, c) DEM simulations.
Spray dried granules are important in the processing of ceramic components as base material for dry compaction shaping operations. Thereby, the flowability of these granules is one important property within processing, especially during die filling in compaction process. In this context the granule properties can have strong influence on homogeneity of the filling and with that the quality of the compacts and finally the sintered products. Also the possible level of complexity of the compacts and the maximum filling and thus processing speed is influenced by the filling behaviour of the granules.

Ceramic granules with adjusted properties were prepared via spray drying. Granule size ($d_{50}$), size distribution and granule density are varied according to the rules of Design of experiments (DoE). By the use of a self-constructed fill device, which maps the process chain: product feeding – fill shoe – die, the filling behaviour of the granules from a moving shoe to a stationary die can be analysed under process-oriented conditions. High speed video is used for visualisation. Via image analysis, filling progress is quantified.

A statistical model had been developed which correlates the granule properties and filling behaviour. The strong influence of the $d_{50}$ and the interaction with particle size distribution will be shown.

I) Visualisation of fill experiment
II) Result of DOE analysis: Interaction plot of $d_{50}$ and Span for begin of the flow $\tau_{10}$
The goal of this research was to develop a model for linking the mechanical and dissolution properties of tablets produced from high shear granules to the process conditions used during the production process. Granules were produced from high shear melt granulation of calcium carbonate powder using polyethylene glycol 1000 as the binder. The process conditions investigated in the granule production process were impeller speed, liquid to solid ratio. The effect of maximum compression force during compression of the tablet and granule size was investigated also investigated. Two methods, Artificial Neural Networks (ANN) and Design of experiment (DoE) were applied to develop models for predicting the mechanical properties form the process and formulation conditions during granulation and tableting processed. These models were tested on unseen, independent data set to evaluate their performance; both models were able to predict at least 65% of the unseen data with R2 values of greater than 0.89.

Figure 1: Comparison of the ANN and DoE models on the predication of tablet porosity.
174. REAL-TIME PREDICTION OF POLYMER-COATED MULTIPARTICULATE DISSOLUTION AS A FUNCTION OF PARTICLE SIZE GROWTH USING PROCESS ANALYTICAL TECHNOLOGY

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To evaluate the effectiveness of in-line measurement of particle size as a predictor of dissolution performance as compared to predictive modelling and offline methods. The Eyecon2 Particle Size Analyser (Innopharma Technology) is used on a GPCG2 Fluid Bed Processor(Glatt) with 6-inch Wurster insert, using both aqueous and organic-based coating solutions / suspensions in the form of Colorcon’s Sure Release and Opadry EC. The Eyecon’s real-time results at multiple weight gains / coating thicknesses are correlated against predictive model results for particle size growth during the coating process, off-line particle size measurement, and real dissolution results as a means of assessing the effectiveness of each technique as a predictor of real-world dissolution results.
175. PARTICLE SIZE MEASUREMENT IN TWIN SCREW WET GRANULATION; AN ANALYSIS OF THE VALUE OF IN-LINE AND AT-LINE MEASUREMENT DATA

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This presentation examines the data collected from both in-line and at-line measurement methods during the execution of a DOE aimed at quantifying, using a data-driven approach, the effects of input parameter changes on a twin screw wet granulation process (Thermo Fisher Scientific, Pharma 11) with a typical pharmaceutical formulation. The results between the PAT tool used (Eyecon2) and at-line tools (sieve analysis and Eyecon1 in its at-line configuration) are contrasted to understand the relative values of each. The real-time quality of the PAT data is also examined in order to further understand the time taken by the process to reach steady state and to understand the inherent variation within the process while at steady state. The effect of these variations on sampling-based measurements is also examined in order to further understand the time taken by the process to reach steady state and to understand the inherent variation within the process while at steady state.

Learning Objective 1- The results between the PAT tool used (Eyecon 2) and at-line tools (sieve analysis and Eyecon 1 in its at-line configuration) are contrasted to understand the relative values of each.

Learning Objective 2 - With the ongoing interest and growth in the continuous manufacturing sector the effective application of PAT can net enormous benefits in process understanding and efficient DOE.

Learning Objective 3- The real-time quality of the PAT data is examined in order to further understand the time taken by the process to reach steady state and to understand the inherent variation within the process while at steady state.
Roller compaction is the main technique to prepare granules via dry granulation. Ribbon sticking and splitting are the major drawbacks, which can hinder the use of roller compaction for some formulations. This may affect its key advantages in terms of continuity and cost effectiveness. The stress applied during this process mediates both of the desired (intact ribbon) and undesired bond formation (splitting and sticking to roller surface). The aim of this work is to investigate the effects of the applied stress and materials properties on the mechanisms of ribbon splitting and intact ribbon formation (Figure-1).

A range of excipients including; microcrystalline cellulose, mannitol, and anhydrous lactose, were used in this study. They have different properties, and differ in their responses to the mechanical stress applied by the roller during compaction. Techniques such as: single particle hardness test and three points bend test for the ribbon were used in this study.

The results showed an inverse relationship between the yield strength of the powder and the strength of the compacted ribbons. Variations in material properties and process variables give rise to different scenarios of ribbon splitting and sticking during roller compaction.
CAN WE PREDICT HYGROSCOPICITY OF A GRANULATION OR TABLET FROM ITS STARTING MATERIALS?

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Dynamic vapour sorption (DVS) is used to measure the change in weight of a sample on exposure to various relative humidity conditions (% RH) at a fixed temperature. The purpose of this study was to check if the sorption profile of tablet starting materials can be used to predict the properties of a tablet granulation or the finished tablet, and whether the tablet compression process affects the granule moisture sorption profile.

A generic wet granulated tablet formulation was prepared from lactose EP, microcrystalline cellulose EP, starch EP, polyvinylpyrrolidone EP and paracetamol EP (100g batch size). DVS experiments were carried out at using a DVS Advantage (SMS) at 25.0°C (± 0.1°C) 10-90% RH with a mass of ca. 20 mg. Individual components, granulations and tablet samples were tested. Tablets (100mg, 6mm diameter) compacted using the Gamlen D Series Dynamic Powder Compaction Analyzer at a range of compaction forces from 200 - 500 kg. A theoretical model was prepared based on the sorption data from each component and their respective ratio used in the tablet. The theoretical data were compared with the experimental data.

The moisture uptake profiles of the compressed tablets were not the same as those of the input materials. Granulation has a significant effect in sorption profile of both granules and tablets. This may result from changes in surface morphology of the granules during granulation as compared to the physical mix. The experimentally obtained absorption amounts at 50 and 90% RH for the granules were ca. 4 and 30 times higher than expected from the properties of the starting materials showing that the granulation process had substantially affected the moisture uptake behaviour of the formulation.

The hygroscopicity of a tablet or any formulation cannot be predicted and rather should be as the process of making solid dosage form has a significant impact on their sorption profile (as well as their particle size, shape, porosity etc). The properties of the granules and tablets were similar. The intact 100mg tablet compressed at 500kg showed a reduced moisture uptake profile compared with the part tablets compressed at lower compaction forces. This is thought to result from reduced water vapor penetration of the tablets compacted to low porosity.

Figure 1. Gamlen D series compaction analyzer

Table 1. Moisture uptake properties of input materials

<table>
<thead>
<tr>
<th>Sample [Ingredients]</th>
<th>Composition (%)</th>
<th>% (w/w) uptake (Experimental)</th>
<th>% (w/w) uptake (Experimental)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acrisol (MCC)</td>
<td>8.35</td>
<td>4.82</td>
<td>11.38</td>
</tr>
<tr>
<td>Lactose</td>
<td>8.35</td>
<td>0.01</td>
<td>0.02</td>
</tr>
<tr>
<td>Cornstarch</td>
<td>1.71</td>
<td>10.90</td>
<td>19.80</td>
</tr>
<tr>
<td>PVP</td>
<td>0.49</td>
<td>17.50</td>
<td>50.00</td>
</tr>
<tr>
<td>Paracetamol (API)</td>
<td>80.34</td>
<td>0.01</td>
<td>0.02</td>
</tr>
</tbody>
</table>

Table 2. Moisture uptake properties of granules and tablets

<table>
<thead>
<tr>
<th>Sample tested</th>
<th>Predicted water uptake based on components (%)</th>
<th>Experimentally measured water uptake (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Physical mix</td>
<td>0.51</td>
<td>1.30</td>
</tr>
<tr>
<td>Granulate 20 mg Paracetamol Tablet (200g compaction load)</td>
<td>0.75</td>
<td>1.74</td>
</tr>
<tr>
<td>Granulate 20 mg Paracetamol Tablet (500g compaction load)</td>
<td>3.05</td>
<td>48.50</td>
</tr>
<tr>
<td>Granulate 100 mg Paracetamol Tablet (300g compaction load)</td>
<td>3.07</td>
<td>50.00</td>
</tr>
<tr>
<td>Granulate 16 mg Paracetamol Tablet (500g compaction load)</td>
<td>3.10</td>
<td>50.30</td>
</tr>
<tr>
<td>Granulate 100 mg Paracetamol Tablet (500g compaction load)</td>
<td>3.43</td>
<td>22.10</td>
</tr>
</tbody>
</table>
DEVELOPMENT OF A PREFERRED EXCIPIENTS PLATFORM FOR CONTINUOUS TWIN SCREW GRANULATION

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As continuous manufacturing is gaining momentum in the pharmaceutical industry, a lot of research is being conducted on twin screw granulation. The objective of current work is the development of a preferred excipients platform for continuous twin screw granulation.

In this work, the influence of 5 process parameters was investigated on 8 formulations, differing in (i) API solubility, (ii) drug load (5 vs. 50% w/w) and (iii) filler type (lactose vs. lactose/microcrystalline cellulose (MCC) (50/50)). The effect of (i) liquid-to-solid (L/S) ratio, (ii) screw speed, (iii) throughput, (iv) kneading element thickness and (v) distribution of the kneading elements across both kneading zones was investigated for each formulation in a D-optimal DoE. The studied granule quality attributes were particle size distribution, friability, bulk and tapped density and Hausner ratio. L/S ratio was the most dominant factor for all formulations. Kneading elements of 1/4 length-to-diameter (L/D) showed superior properties compared to 1/6 L/D kneading elements in terms of friability, flow properties and the amount of fines. The effect of kneading element distribution and barrel fill level, determined by both throughput and screw speed, was limited within the experimental ranges.

For low drug load formulations, filler properties were more dominant than API properties. Furthermore, lactose/MCC proved a more robust filler than pure lactose towards changes in process settings as well as API characteristics. This is illustrated in Figure 1 for friability. This signifies that a lactose/MCC (50/50) mixture could be used as a placebo formulation during development of low drug load formulations, reducing both R&D time and API consumption in early development.

When drug load was increased to 50%, API properties became more important. Granule characteristics of the poorly soluble API were unacceptable when combined with lactose. Therefore additional granulation trials were performed to evaluate PVP instead of HPMC as binder as well as the addition of SLS.

Figure 1. Friability of low drug load formulations.
ABSTRACT

Regime mapping was done for rehydration for a powder mix systems of crystalline lactose and an amorphous powder (maltodextrin DE19) and crystalline lactose and fat containing powder (creamer) in agitated water. Focused beam reflectance measurement (FBRM) was used to track the rehydration process. Rate limiting regimes for the powder mix systems at different agitation rates were evaluated and mapped. For the lactose/maltodextrin mixes, increasing amount of lactose in the system did not have a linear relationship with rehydration time. The maltodextrin rate limiting step dominated the rehydration process for mixes not containing a large amount of lactose (90 wt%). For the lactose/creamer mixes, increasing amount of lactose greatly improved creamer rehydration. The creamer rate limiting step dominated the rehydration process.

Regime maps generated were used to investigate the effect of agitation rate on powder mix rehydration. This mapping approach can be used to qualitatively assess the solubilisation ability of novel dehydrated food powders which consist of powder mixtures at different process conditions.
In industries such as pharmaceuticals, food and chemicals the final products can be in the form of compacts. In compaction processes, the powder is introduced into a die using linear or rotary feeding systems before being compressed into the compact form using rigid punches. The final properties of powder compacts are determined by the mass of the powder delivered into the die and predicting the flow behaviour of the powder can lead to designing a process and production of a compact with desired properties.

In linear and rotary feeding systems, the powder is discharged into the die under two mechanisms. In gravity fill the powder is discharged under the effect of gravity. As more mass is delivered into the die, increasing air pressure opposes to the powder flow. In suction fill the downward motion of the lower punch creates a suction effect on the powder increasing the mass delivered into the die.

The influence of air pressure conditions on the mass of the powder introduced in die filling process has been highlighted previously [1-4]. In this study, a linear shoe-die system is used to measure the pressure changes in the die during die filling stage under gravity and suction fill mechanisms. The effects of shoe and suction velocities on the mass delivered into the die are examined with respect to the differential pressure between the die and ambient atmosphere. An existing model for prediction of the mass introduced into the die under gravity fill mechanism is examined. This model is modified to include the influence of powder height in the die and the differential pressure developed. This model is modified further for suction fill mechanism.


Solid pharmaceutical tablets can be manufactured via three processing technologies: direct compression, dry granulation and wet granulation before the final compaction process. Dry granulation using roll compaction generally involves production of ribbons, followed by milling to produce granules and the production of tablets. The mechanical properties of ribbons produced during roll compaction can influence breakage behaviour in a mill and hence the performance of a drug formulation. Therefore it is important to explore critical factors that determine the quality of ribbons.

In this study, MCC Avicel PH-102 was used as the model powder for roll compaction and the critical operating factors affecting ribbon quality were studied. MCC 102 ribbons were manufactured at a range of process conditions (roll speed, feed screw speed and compaction pressure) using the TF mini roll compactor with a serrated die & punch (DPS), grooved roll surface. The key ribbon properties measured are the powder feed ratio (defined as the ratio of feed screw speed to that of roll speed) and mass throughput ratio (defined as the mass of ribbons produced in a given time to that of fines).

The porosity of ribbons was observed to depend significantly on powder feed ratio into the compaction zone. Porosity remained constant at a fixed feed ratio irrespective of the absolute roll speed and the feed screw speed conditions used. Mass throughput ratio is another factor that was introduced to describe process efficiency i.e. to draw comparison between the amount of ribbons and fines. The amount of ribbons and fines generated at a given process condition depends significantly on the feed screw speed and the compaction pressure. In addition, ribbon porosity decreased with increasing pressure but there was negligible effect on ribbon porosity when excessively high pressure (> 60 bar) was used. Ribbon porosity was also observed to decrease with increasing feed screw speed but the converse is true with increasing roll speed.

In conclusion, the impact of various roll compaction process parameters were critically investigated and a detailed insight into the main factors (powder feed and mass throughput ratios) that govern the behaviour of roll compacted ribbons was provided. In future, the focus is to relate these process properties (and ribbon porosity) to granule size distribution from a milling process.

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Steam-jet granulation is a process used in dairy industry to produce instant agglomerated milk powder. Agglomerated instant powders exhibit improved wettability and rehydration behaviour, which are essential attributes for coffee whiteners applications. Although there is a growing interest for research in this area, the steam-jet granulation process has been little studied to date and the quality control at industrial scale remains experimental and empirical. Moreover, the multi-factorial causes at the root of the rehydration properties of the final agglomerates make it difficult to identify the key process parameters that should be controlled to meet the quality requirements.

The present study investigated industrial data to study how different raw materials properties and process parameters interact and contribute to the production of skim milk agglomerates with improved functional properties.

Dynamic vapour sorption and differential scanning calorimetry were used to characterize both the native raw materials and the agglomerated powders. A multivariate data analysis was used to identify correlations between the raw material properties, the process parameters and the physicochemical and functional properties of the products. The water content of the native raw material and the post-drying temperature were found to be critical in controlling the humidity and thermodynamical properties (glass transition temperature) of the agglomerates. These properties were correlated to the wetting time and showed their significant influence on the rehydration behaviour of the agglomerates. Recommendations concerning production parameters are given to avoid conform rehydration behaviour in industrial agglomerated skim milk powder.
Evaluating rates of shearing at different shear velocities is the focus of this study, with the aim to characterize the shear flow in a periodic unit shear cell system. The large particle of interest is the model particle of the single granule. The number of bulk particles is the model particles of small glass beads which enable creating the shear condition in the system.

The upper and lower plates were made of stainless steel particles. The upper plate was set to be in stationary condition and the lower plate was moved for shearing the bed particles. Shear velocities between 7.33 and 14.66 m/s were predefined to indicate the range of speeds used in the annular shear cell. The DEM simulations were performed using LIGGGHTS, an open DEM code software. The material properties and parameters used in the DEM simulations were identified. From this study, varying the shear velocities produced different bed height between the plates and rates of shearing. It is expected that this preliminary study can give a good starting point for studying the future granule breakage under shear deformation.
In the pharmaceutical industry, granulation is considered to be a key operation that determines the quality of the final produced tablet. Among the granulation types, twin screw granulation (TSG) as a wet granulation has been widely used. Drying process is a necessary and vital step after a wet granulation processes. Commonly, fluidized bed (FB) has been used to dry the produced granules. The aim of this study is to produce granules from TSG and investigate the FB drying process parameters on the final properties of granules and tablet.

Granules were tested for their size distribution and moisture content before and after drying in FB, at different process parameters. Fluidized bed (Glatt WSG-3) was used to dry the granules at different air velocity (2, 2.6 and 3.4 m/s) at 50°C. It was found that the size distribution of granules decreased during drying in FB in comparison to the original granules. This gave an indication of breakage of granules while drying in FB, which resulted in size reduction. It was also found that increasing the air velocity during drying in FB increased the extent of granules breakage, which resulted in higher size reduction. The granules before and after drying were compressed, and the tablet strength was correlated to the difference in process parameters in fluidized bed drying. It was found that tablet produced from fresh granules (directly from TSG) were stronger. The tablets produced from granules dried in FB resulted in lower tensile strength compared to that of fresh granules. The difference in strength of tablet at different drying parameters is due to the difference in moisture content and size distribution of granules.
Wet granulation processes are difficult to reproduce and thus are often operated inefficiently which leads to high recycle rates in a continuous processes and high rejection rates in batch processes. A modelling approach can help to improve the efficiency of wet granulation processes significantly by understanding the effects of process parameters and material properties better.

In this study, a compartment-based model is used to model the wet granulation process, employing a multi-dimensional population balance framework. For this modelling approach, the mixer is decomposed in three regions spray region, impeller region, and chopper region. Laboratory scale granulation experiments are conducted to estimate unknown parameters for empirical rate expressions. Finally, the model developed is preliminarily validated using experimental data.

In future work, it is intended to couple the population balance model to a discrete element model. Discrete element modelling is a mechanistic approach to predict particle behaviour.
Powder with liquid systems are prevalent in many industrial processes including granulation and coating. In these processes, liquid is added and dispersed into bulk dry powder which can significantly affect the flow behaviour. To simulate wet particles with small amounts of liquid, liquid bridge forces consisting of viscous and capillary forces [1] are incorporated into Discrete Element Method (DEM). Despite the advances in computational power over recent years, simulating actual industrial processes which could have over billion particles is still difficult and scaled-up or coarse grain particles are often used to speed up computations. Several authors have proposed coarse grain models to simulate the original particle behaviour adequately, particularly for dry cohesionless or dry cohesive particles, e.g. by Sakai and co-authors [2-3]. Here, we investigated several coarse grain models including Sakai's model for DEM with liquid bridge force, i.e. for wet particles. The wet particle flow in a typical mixer granulator is simulated to compare and evaluate these coarse grain models.


The rice protein has raised interest due to its unique nutritional value (rich in essential amino acids) and nutraceutical properties. This protein is gluten and dairy free which make it a hypoallergenic ingredient. However, the rice protein concentrate (RPC) powder presents fine particles and poor instant properties, limiting its use. In order to outline this issue, the agglomeration process is highlighted as an alternative to produce instant rice protein concentrate. Conventional fluidized beds are widely used for wet agglomeration. This process involves spraying a binder solution onto the moving particles, resulting in the particles growth and drying. The use of a suitable binder solution during the agglomeration process of rice protein concentrate is required to not modify the nutritional value of the final product. The use of a suitable binder is essential to not modify the nutritional value of the final product. Konjac glucomannan (KGM) is a plant-derived polymer obtained by extraction from the tubers of *Amorphophallus konjac K. Koch*. It has been widely used in food, pharmaceutical, biomedical, and engineering fields, owing to its excellent gelling properties. In addition, the KGM is an edible product and can be a promising natural polymer to be used as a binder for RPC agglomeration, providing the non-use of adjuvants substances like simple carbohydrates. The in-line particle size monitoring during an agglomeration process is desirable, since this is one of the key characteristics of an agglomerated product. The application of the Spatial Filter Velocimetry (SFV) as a process analytical technology (PAT) tool for in-line particle size monitoring in fluidized bed agglomeration of pharmaceutical products is already under investigation, but this use in agglomeration of food products is in the early stage.

In this work, the fluidized bed agglomeration of RPC fine particles using KGM as binder is investigated as a potential method to produce an instant food powder. Aqueous solution of KGM (0.5% w/w) was used as binder at a flow rate of 2.0 mL/min and atomization pressure of 69 kPa. The air temperature was set at 75 ºC. The agglomeration was stopped when 80 mL of binder was atomized, after that, the product was dried. The particle size was monitored in-line by a SFV probe. The agglomeration of RPC using KGM solution as binder could be successfully carried out in a fluidized bed, resulting in an instant food powder with desirable moisture content (about 3.5% w.b) and flowability improved. RPC agglomerated presented a median particle size 5 times larger than those of the raw RPC. This increase of the particle size provided an enhancement of instant properties, which was characterized by the lower wetting time when compared to RPC before the process. These results suggest that KGM can be a powerful binder to agglomerate RPC or other powder protein, avoiding the use of simple carbohydrates for this purpose. The in-line particle size measurements provided a better understating of the particle growth evolution. This indicates the potential use of the SFV probe as a Process Analytical Technology tool for the particle size monitoring in fluidized bed agglomeration of food powders. The RPC agglomerated powder produced presents a high potential to be used as an ingredient in food or pharmaceutical formulations.
COATING OF PHASE CHANGE MATERIALS (PCMS) IN FLUIDIZED BED

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Thermosensitive products that are susceptible to microbiological contamination or that require conservation of temperature to provide sensory attributes are very common in the food industry. The application of thermo active packaging to the food sector is still very incipient despite presenting high demand, and its development allows to reduce the effects of thermal variations during transportation, storage and consumption. A possible way to increase the thermal capacity of a package and maintain the product at the desired temperature is through storage of thermal energy by incorporating phase change materials (PCMs) into the structure of the packaging material. However, PCMs must be encapsulated to contain the volumetric variation that occurs during the solid-liquid phase transition, preventing mixing with the packaging material. Coating in fluidized bed, although simple and scalable, is restricted to solid state PCMs and their phase change temperature. Carnauba wax, besides being non-toxic and allowed in food, has a high enthalpy and melting point value. Therefore, this work aimed to coat carnauba wax particles in fluidized bed. Carnauba wax particles were produced by cold and free solvent extrusion. A selection of coating materials was performed based on their rheological and adhesive characteristics, and after it was validated in coating tests. Suspensions containing sodium alginate and Eudragit® showed the lowest contact angle and low viscosity, and were able to contain the volumetric variation of the particles (coating efficiency = 60%). Coating materials with contact angle above 58 ° and high viscosity did not cover the particles. From this study, it is possible to obtain the understanding of the process of coating meltable particles in fluidized bed, expanding to other PCMs and enabling the functionality of textile materials, construction and food packaging.
CHARACTERIZATION OF SELF-ASSEMBLED NANOSTRUCTURES IN SPRAY-DRIED DETERGENT POWDERS

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Typical laundry detergent powders were produced by spray drying aqueous slurries containing linear alkylbenzene sulfonate (LAS), sodium sulphate and sodium silicate. These powders have a complex, multiscale structure. The inorganic salts, e.g., sodium sulphate, tend to form clearly defined crystallites which are distributed within a continuous matrix dominated by self-assembled surfactant structure e.g. lamellar phases (Fig. 1). In this study the influence of the initial water content of the slurry and the alkaline sodium silicate ratio (nSiO₂: Na₂O: where n is the ratio) on the polymorphism, crystallite size and degree of crystallinity of sodium sulphate was probed using a range of techniques including FTIR, Raman spectroscopy, and wide angle x-ray scattering. Additionally, the phase behaviour and conformational order of self-assembled structures were investigated using small angle x-ray scattering (SAXS) and Infrared spectroscopy respectively.

LAS surfactant molecules were observed to form lamellar phases and the spacing of the lamellar, d-spacing, was found to decrease on addition of sodium silicate to the formulation. The results of FTIR indicated that this change in d-spacing value was in concomitant with an increase in the degree of conformational order of hydrocarbon chains in LAS molecules. The presence of sodium silicate was also observed to result in the formation of sub-micron, needle like crystals of the meta-stable polymorph of sodium sulphate (phase III). These findings were in good agreement with spectroscopic data suggesting more disorder in the crystallinity of the sulphate.

Figure 1. Experimental SAXS data illustrating the presence of lamellar phases in spray-dried detergent powders (left), and WAXS data showing the presence of different polymorphs of sodium sulphate (right).
IDENTIFY SOLID AND GAS FLOW PATTERNS IN BUBBLING FLUIDIZED BED AND THEIR IMPACT ON SOLID MIXING BASED ON OPERATIONAL CONDITIONS

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Bubbling fluidization has been widely applied in industrial processes, such as granulation, coating, mixing, power generation from coal, renewable energy production, gasification and pyrolysis. In this study, we attempted to predict solid and bubble flow patterns in a bubbling fluidized bed based on operational conditions, the air distributor and particle velocity, and investigated then the impact of flow pattern on solid mixing behaviour. The solid mixing behaviour was estimated based on the dispersion coefficient of particles, the active index (AI), and the distribution of particle residence time within the entire bed. It was found that the flow patterns are a result of a combination of operational conditions, properties of bed materials, and bed designs. A ‘Flow Pattern Parameter (FPP)’ was proposed to identify the solid flow pattern in a bubbling fluidized bed. Different flow pattern corresponds to a certain range of the Flow Pattern Parameter. The particle dispersion coefficient, AI, and the distribution of particle residence time clearly agree with solid flow patterns and bubbling behaviour within the beds.

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FPP = \frac{H}{D} \sqrt{\frac{u^2}{d_D^4 (u-u_{mf})^2}} = \frac{H}{D} \frac{|v|}{d_D^2 (u-u_{mf})}
\]

The ‘Flow Pattern Parameter (FPP)’ consists of particle kinetic energy, bed aspect ratio \((H/D)\), pore size of air distributor, minimum fluidization velocity, and superficial gas velocity. The results show that solid flow patterns in the bubbling fluidized bed can be clearly classified based on the Flow Pattern Parameter. Different flow pattern corresponds to a certain range of the Flow Pattern Parameter.

Figure 1. Solid flow patterns.

Figure 2. FPP vs. \(u-u_{mf}\), where \(v^2\) for \(\cdots\) (H/D=1) & \(\cdots\) (H/D=2) is 0.2 \((m/s)^2\), for \(\cdots\) (H/D=1) & \(\cdots\) (H/D=2) is 0.5 \((m/s)^2\).