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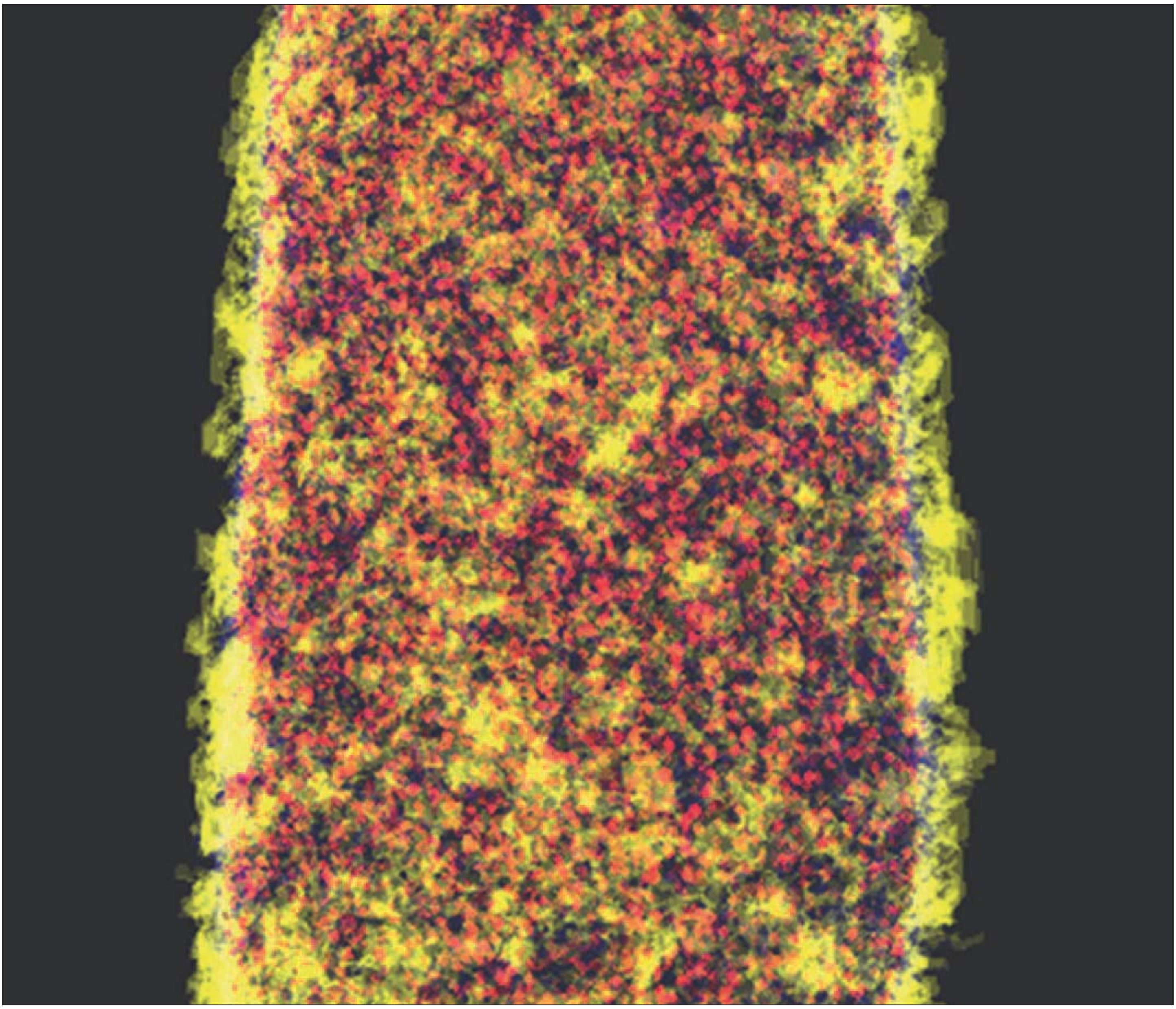

Computer-Aided Design of Pharmaceutical Formulation

Computer-Aided Design of Pharmaceutical Formulations: F-CAD Software and a Mathematical Concept

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Introduction

Within the past decade there have been several attempts made by controlling organization such as FDA and EMEA to place pharmaceutical production and formulation R&D on a higher level of excellence, and as a result new motivation slogans. One of the current slogans spread among major pharmaceutical companies is "Right First Time", meaning that the market-ready formulation has to be developed and fixed at very early development phases, i.e. pre-formulation. However, a closer look to the generally accepted workflow during pharmaceutical R&D, scale-up (1), product launch, etc. of a solid dosage form, reveals, that the situation is far from ideal. In fact, the first clinical trials of a new active substance start in general with a "service" dosage form – often a capsule formulation –, which is not identical with the "prototype" formulation in a later clinical phase, when the marketed dosage form is realized – often a tablet formulation (2). Such a preliminary "service" dosage form cannot comply with the idea of "Right First Time". The subsequent follow-up activities, the fast prototyping, the bioequivalence testing, the scale-up procedures add additional uncertainties. All those factors slow down the process of time to market and yield finally a 2–3 sigma manufacturing performance. If there is a goal for a final six-sigma quality of the marketed dosage form, it is mandatory to start the clinical phase I with the desired final marketed dosage form (3). Thus, no service form and subsequent bioequivalence testing is needed. Long-term stability testing, with the right formulation can be started at the time of the first clinical trial. This ambitious goal is best achieved by applying a concept of computer-aided R&D, which means the replacement of lab work by a computer. This paper describes a mathematical concept and the software F-CAD used for substitution of laboratory experiments during all phases (3) of the design and development of new pharmaceutical products.

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Cover page: Computer model of tablet dissolution

Cellular Automata as models for natural phenomena

Cellular Automata (CA) as a mathematical concept were introduced by Ulam and Von Neuman in 1940s. Since that time, the CA-based models were developed and applied for modeling of a wide spectrum of natural phenomena (4). The success of the application of CA in different domains is mostly related to its ability to take into an account local interactions between spatial domains of different kind. For example, Conway's game of life, where CA cells are representing a biological cell or bacteria with strict rules for multiplication or death in dependence of a number of neighbors surrounding the target cell (5). Despite the apparent simplicity of the rules used with CA models, the resulting structures for larger sets of cells are very complex and are very well approximating the corresponding natural phenomena.

Natural phenomena are often evolutionary, i.e. the development and changes of a system is happening iteratively, the every new generated result is the result of a certain operation of the previous ones. One of the most remarkable examples is the sea shell patterns development (6). On the Figure 1 the photograph of a sea shell is shown, featuring characteristic pattern along with the result of simple one-dimensional cellular automata-generated pattern. It is possible to draw a number of stunning examples where CA-based models are capable of imitating the behavior of natural systems, from crystal growth to biological objects, sociology and flow simulations (4,7).

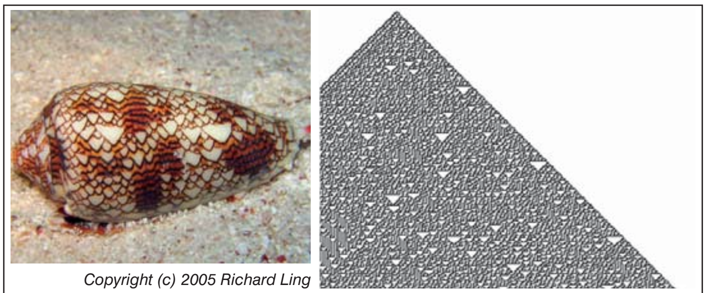
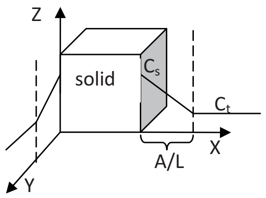


Figure 1. Natural pattern of a dangerous sea snail (Conus textile), left and the pattern of one-dimensional cellular automata generated with rule 30 (4)

Considering the properties of a CA model to describe the natural phenomena, an attempt to use CA for calculation of drug dissolution was made at CINCAP in 2007. The first software prototypes were tested at the University of Basel (7). Despite of a limited computational power at that time the models of drug release from three-dimensional CA-matrixes were capable of generating realistic release curves. Further development of this approach at CINCAP has resulted in a full-featured software package for design, development, and testing of formulations with very limited amount of experimental workload (8).

F-CAD as software to model complexity of solids compaction and dissolution

F-CAD is a software package, i.e. a set of several stand-alone software products serving individual design tasks. The central part of the software is the CA-based mathematical model for calculation of a release profile from individual particles in a simulated pharmaceutical compact. The calculation model is based on the generalized description of the solid-liquid interface as depicted on the Figure 2 and corresponds in general to Noyes-Whitney equation. Solid particle or a crystal is represented by one or more of the individual cells, where each cell bears a unique rule set which guides its state changes. In presence of dissolution liquid, the solid cell is gradually changing its state, i.e. if the liquid film which is surrounding the solid has concentration below saturation, the solid particle will lose its weight by a defined value. This process is repeated for all faces of the solid particle exposed to the liquid. When there is nothing left of the particle, it is converted to the liquid with residual concentration. The rate at which the solid is transferred to the solution is governed by a rate constant; its value is determined for every new API through a calibration process. Important to note, that the same rule set is applied for all of the solid particles involved in the formulation, i.e. for every API and excipient taking in account particle size and particle size distribution. Presence of excipients in the formulation can significantly change the pattern of a release profile; this is valid for the simulated formulations either. For example, a swelling excipient particle upon contact with liquid will occupy the liquid cell by swelling. The rate of swelling is yet another constant which is unique for every hydrophilic excipient and to be determined through a calibration routine. Important is to note, that the calibration routines for F-CAD should not be repeated every time the system is used. Once the constants were determined, they can be used in further projects.



$$\frac{dC}{dt} = \frac{DA(C_s - C)}{L}$$

Figure 2. Schematic representation of a diffusion layer model of a solid-liquid interface. Noyes-Whitney equation is shown on the right.

Despite the fact that the dissolution profile calculation is a central part of F-CAD mathematical kernel, the particle arrangement algorithm is yet another essential part of the whole system. Unlike the natural compression, where the powder is first loaded into a die and then compacted due to the volumetric shrinkage, the F-CAD particles are "grown" to the target mass and size distribution within a final, desired, and rigid tablet volume.

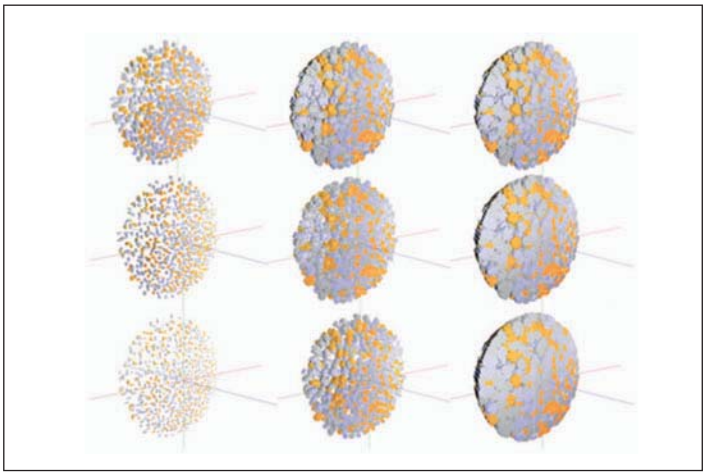


Figure 3. Growth of particles in a simulated tablet: bottom left – seeds; bottom-right – grown particles after 9th iteration.

This processing step is by step illustrated on the Figure 3. The "growth" process starts at "seeding" the initial germ-particles of 3 individual cells in the centers of the future particles. The locations of the centers particles are determined by the sphere packing algorithm. The initial centers will remain the barycenters of the developed particles. The spatial shift might occur due to constraints forces the particles to rearrange their locations and shapes. Once the centers are positioned, the subsequent "growth" process is governed by CA rules which are transforming the initial seeds into spherical objects. At this point growth is continued until the particle does not meet the boundary or another growing particle. At this event, the diametrical growth is stopped, but the particle is trying to allocate the gained mass at the nearest empty place, i.e. the particle deforms.

This approach is allowing the simulation of a higher tablet density at the vicinity of contact surfaces, in the similar way as it happens in reality during the compaction process. The Figure 4 shows the development of the solid structure rendered for visualization purposes at lower resolution, as a visualization of reduction of the porous network down to individual porous domains

The overall efficiency of such inverted approach to compaction simulation is delivering very realistic and robust results if applied to hundreds of millions of cells as shown in the following example. The renderings from computer memory for tablets where the active ingredient was removed are shown on the Figure 5 a,b,c. On the left of each photo the real tablet with washed out API (caffeine) is shown (9), whereas on the right the corresponding result of a CA-based growth mechanism of particle arrangement and compaction simulation. The simulation was performed for 3 different size-fractions of the API and were visually compared with their real counterparts (see Figure 5 a,b,c).

The particle size distribution of the simulated granules or particles is varying during the growth steps. The resulting distribution function resembles the realistic figures, see Figure 6. It could be expected that the size distribution function would be not very different to delta-function due to homogeneous time steps and equal rules application during the growth process, however the heterogeneous and iteration-dependant constraints (walls and neighboring particles) are changing the distribution function to Gaussian or similar type.

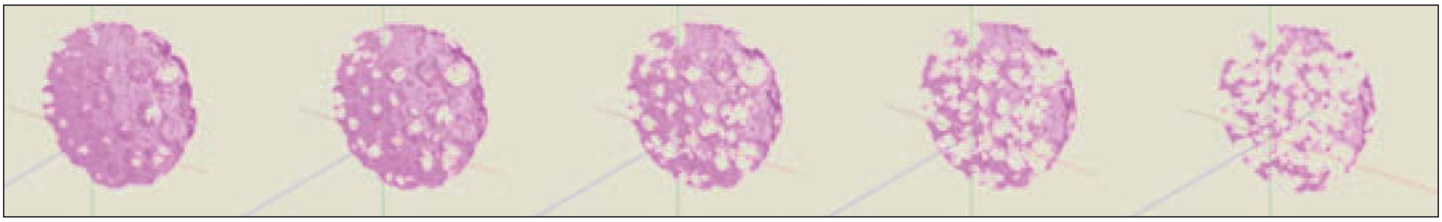


Figure 4. From left to right: Reduction of a porous network (pores depicted as pink) during growth of solid particles (solids are transparent).

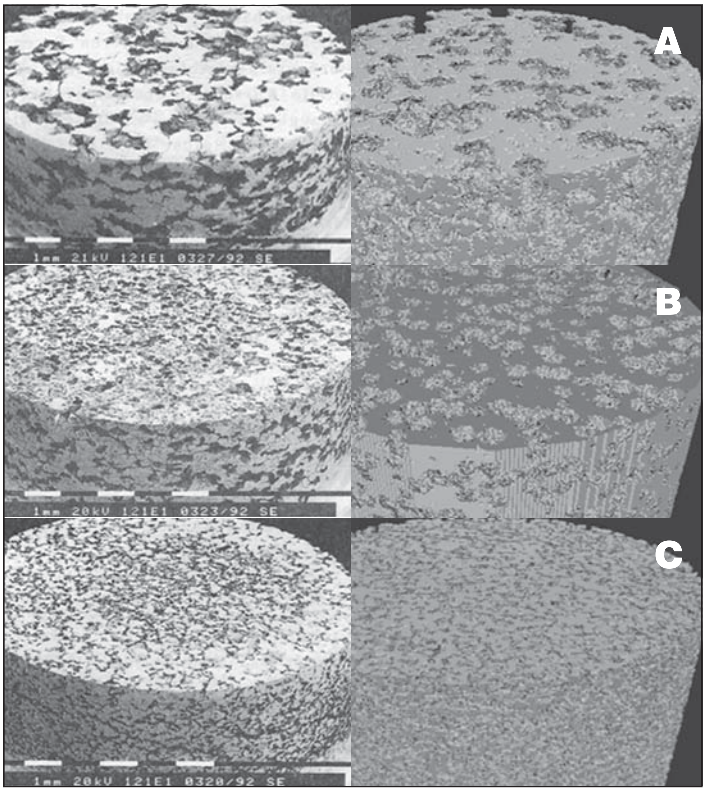


Figure 5. Computer-generated tablet (left) and real tablet with leached out API (caffeine) (9); From top to bottom: a) Caffeine 500-710 µm, b) Caffeine 250-355 µm, and c) Caffeine 125-180 µm.

The dissolution and compaction models are the two main parts of the F-CAD software. However, the software consists of other auxiliary modules to allow correct calculation task design and management.

The typical work flow with F-CAD involves employment of different module combinations allowing an application of F-CAD for large variety of tasks in formulation design.

F-CAD modes of operation (general schema):

A generalized task design and operation workflow consists of 3 main phases: 1) 3-dimentional design of a tablet geometry in order to define the wall constraints; 2) packing the components into the hollow tablet; and 3) calculation of the release profile.

In case of a new active substance, which was never used with F-CAD calibration is mandatory. The calibration of an ingredient, - API or an inactive excipient, - is usually carried out with laboratory experiments for an intrinsic dissolution rate (IDR) data. The IDR profile is attempted to be simulated by F-CAD using the dissolution constants at first approximation. In case the resulting release profile has deviation from the laboratory data, the optimization algorithm (Nelder-Mead simplex method) is used to find the solubility constant where the experimental and calculated release profiles converge taking in account the type of dissolution test (paddle, basket, rotational speed) and type of solvent (artificial gastric juice, pH, ionic strength, surfactant etc).

Figure 7 is a screenshot of the TabletDesigner software module illustrating the view on created tablet geometry. The shape of a tablet is not limited to classical ovals or circles but enables complex geometries. The software calculates automatically the volume and surface of the resulting compacts.

The resulting 3D-shape of the tablet is later converted into matrix representation to be used with particle arrangement and compaction module.

The second stage of computer-aided experiments with F-CAD is an arrangement of particles and their locations in a designed geometry. This step is utilizing the growth algorithm to place the particles as it was described earlier. At this stage, the different unit operations such as direct compaction, respectively wet granulation, result in differences in particle sizes and different particle arrangements, which need to be taken into an account. Whereas the direct compaction assumes intermixed particles of API and excipient to form a compact, the wet- or dry-granulation process clearly specifies the inner and outer phases. In order to simulate granular arrangement of particles and corresponding release-profile changes, the "Swiss cheese" procedure was developed at CINCAP. Following its name, the "Swiss cheese"-structure is about to be developed by growing only granules until a specified or desired size distribution. Once the granules are created, the remaining space is filled completely with auxiliary (starting) material (keeping its initial size) and the larger-sized granular material is removed. The remaining structure is very much resembling the Swiss cheese, hence its name.

The holes in the "cheese" are filled with composition of the inner phase and the auxiliary material is exchanged with the composition of the outer phase of the tablet formulation. The Figure 8 shows the release profiles of two identical compositions, where the only difference in the formulation consist of the unit operations involved: one simulates direct compaction and the other one is granulated.

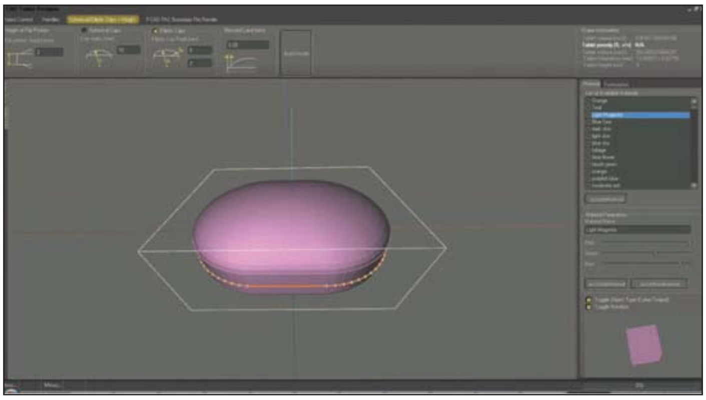


Figure 7. Screenshot of TabletDesigner.

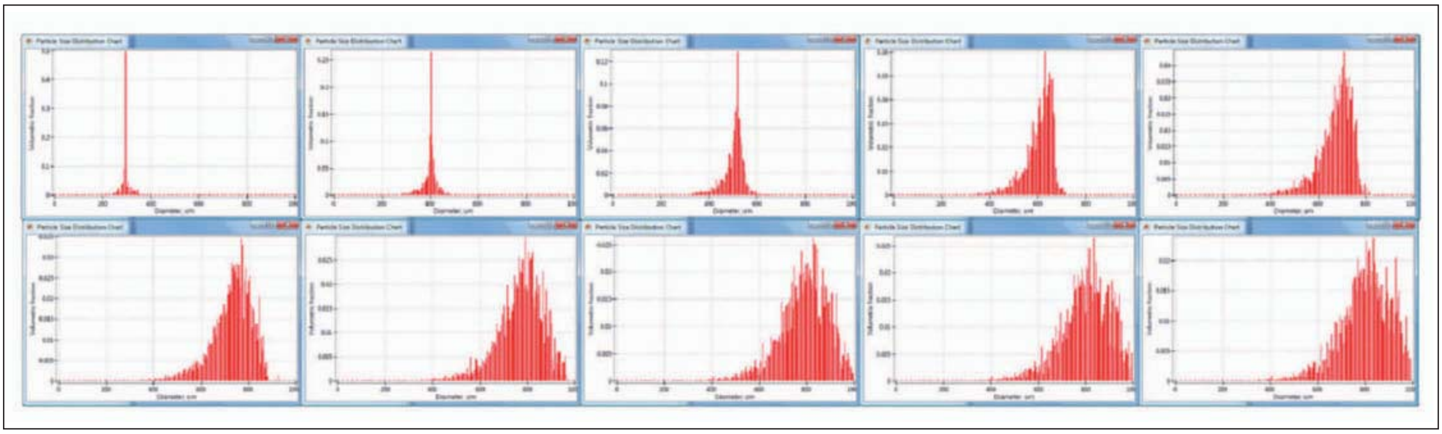


Figure 6. Particle size distribution of individual particles in a compact with respect to growth iteration (top-left: initial set, bottom right: after 10th iteration)

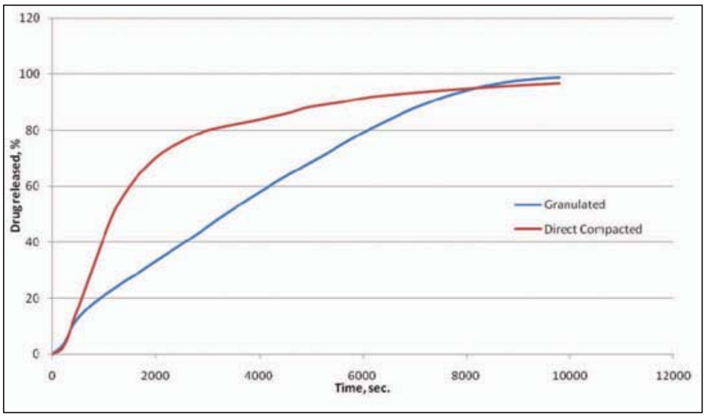


Figure 8. Release profiles generated for two different unit operations: direct compaction and wet granulation. Both are simulated curves, the formulation compositions are identical.

This example shows that release curves could show significant differences depending on the unit operation employed and the F-CAD computational models are giving a good approximation for investigation of the unit operation influence on the final release profile of the drug.

Testing of the release profile

The release profile of the API is calculated for each time point in accordance to initial set of conditions. The rules for CA matrix are applied at each iteration step, and the statistics of CA-cells count is collected. The amount of drug released is calculated in accordance to the number of cells which have changed their state from solid to liquid.

Figure 9 shows the calculated release profile from caffeine model formulations in comparison to the laboratory-obtained data. Unlike simple model fitting, the CA-based models of the release profiles are capable of assessing a formulation –induced deviations from the mean, i.e. an error. This is due to random distribution of particles during particle arrangement stage. Indeed, in case of heterogeneous distribution of granule sizes of individual compound, the release kinetics could be significantly altered by the particles located right on the surface, i.e. in direct contact with dissolution media. This effect is taken by the CA-model into an account and is illustrated on the Figure 10. The enlargement section of the simulated release profile is showing the release of the drug which is located directly on the surface of the compact. Usually, these effects are overlooked for immediate release formulations due to sampling times resolution; however, extended release formulations with hydrophilic matrixes have often displayed an initial "burst" effect which is governed by a fast penetration of a dissolution media into the surface layer of a compact.

Another important property of a pharmaceutical compact is its shape. The shape adjustments are often required not only due to marketing issues, but coating necessity, etc. However, a formulation might be sensitive to the shape alterations; hence changes in the release profiles are expected. The CA-based models of drug release emulation are capable of displaying the shape-effect on the

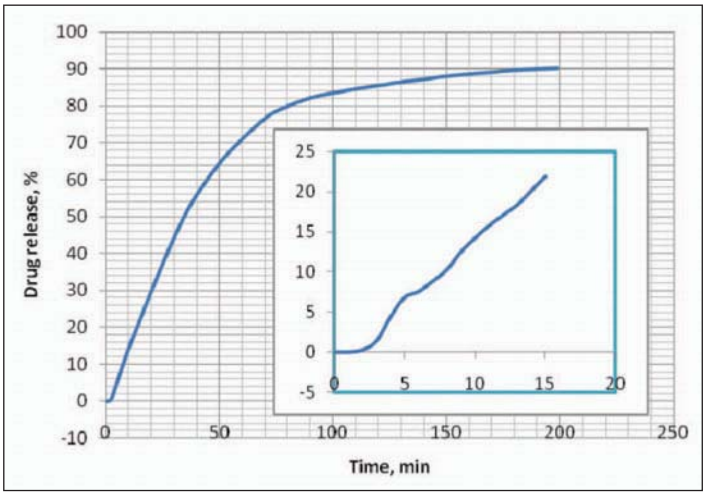
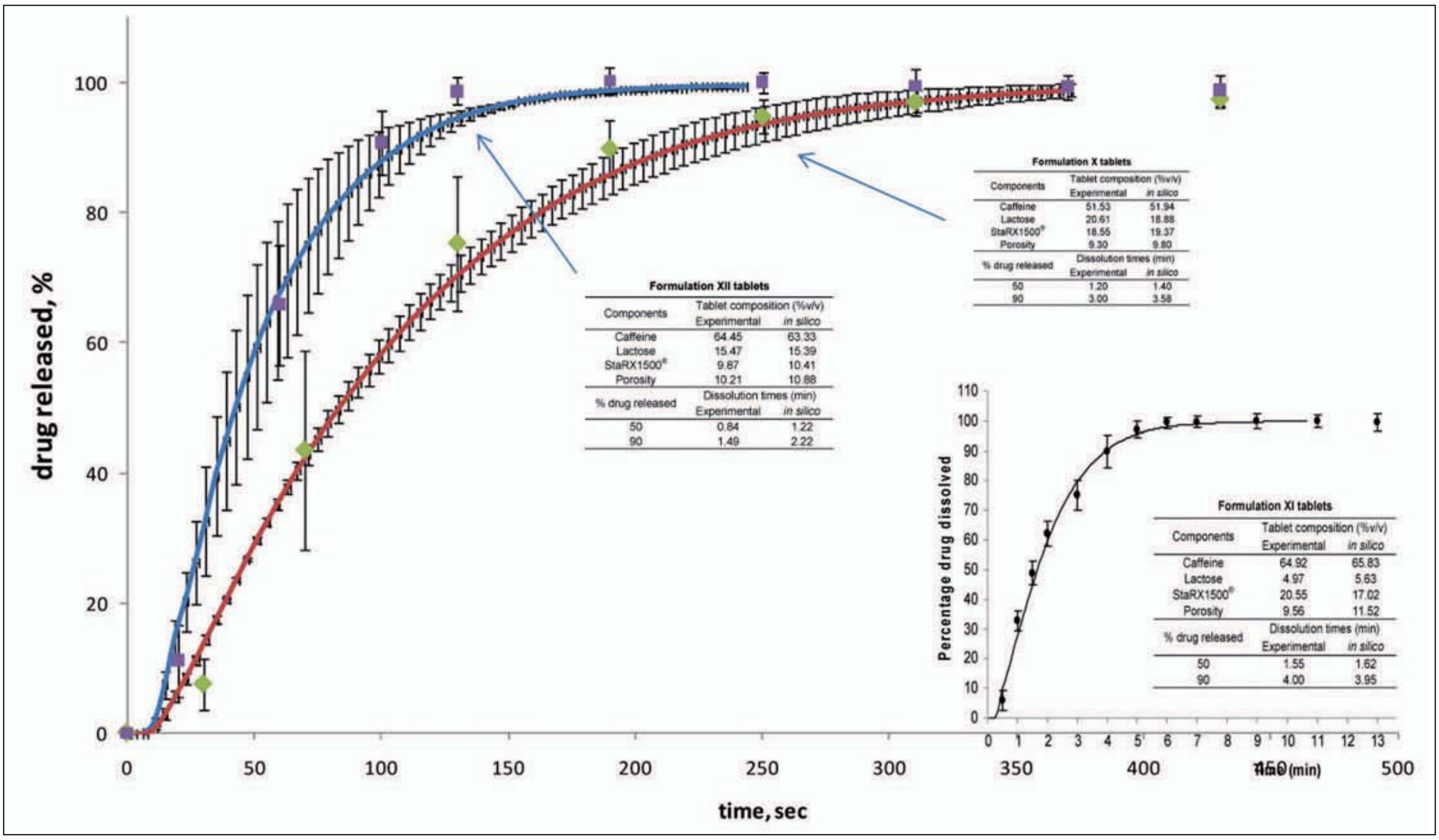


Figure 10. Arbitrary simulated formulation release profile with an enlargement of first 15 minutes. The "drug on surface"-effect is expressed on the 5th minute of the release curve.



Formulation X tablets

Components	Tablet composition (%v/v) Experimental	*in silico*
Caffeine	51.53	51.94
Lactose	20.61	18.88
StaRX1500®	18.55	19.37
Porosity	9.30	9.80
% drug released	**Dissolution times (min) Experimental**	***in silico***
50	1.20	1.40
90	3.00	3.58

Formulation XII tablets

Components	Tablet composition (%w/v) Experimental	*in silico*
Caffeine	64.45	63.33
Lactose	15.47	15.39
StaRX1500®	9.87	10.41
Porosity	10.21	10.88
% drug released	**Dissolution times (min) Experimental**	***in silico***
50	0.84	1.22
90	1.49	2.22

Formulation XI tablets

Components	Tablet composition (%v/v) Experimental	*in silico*
Caffeine	64.92	65.83
Lactose	4.97	5.63
StaRX1500®	20.55	17.02
Porosity	9.56	11.52
% drug released	**Dissolution times (min) Experimental**	***in silico***
50	1.55	1.62
90	4.00	3.95

Figure 9. Calculated (solid lines) and experimental release profiles for different caffeine formulations (7).

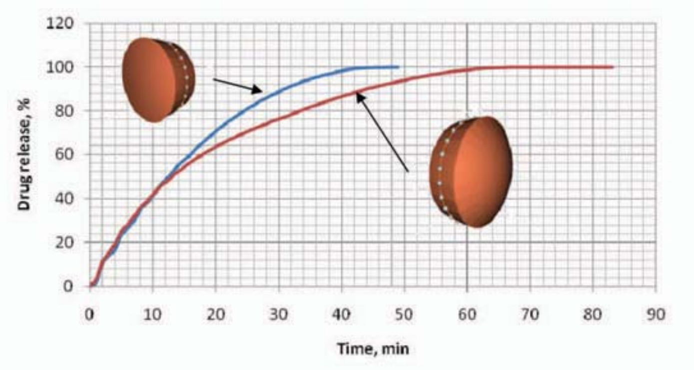


Figure 11. F-CAD-generated release curves for identical formulations, identical porosities, masses, and compact volumes. The difference is shape of two compacts: flat round vs. round concave.

release profile. The calculated release profiles for identical formulations and identical compact volumes and porosities are shown on the Figure 11. This property of the CA-based release models is very helpful for research works on geometrically-controlled drug delivery devices and formulations.

Input data

Generally required dataset for successful development with F-CAD is not exceeding the normally available data. The API-related data include solubility and stability profiles at different pH-ranges; true density, particle size distribution. In case of known polymorphs, the same set of data should be readily available for different polymorphic modifications. For calibration purposes the intrinsic dissolution rates (IDR) for an API of interest are required. The excipients used need to be investigated as well for their particle sizes, true densities and an effect they cause on the API solubility. The latter is usually accomplished by studying the IDR of binary mixtures between an excipient and an API of an interest. For simplicity the IDR of a trial formulation consisting of the API and of excipients of interest, which need to be chemically compatible (3), - is often tested at first. Important is to note that once being characterized an excipient can be further used with different APIs and excipient mixtures.

Conclusions

F-CAD system and its mathematical concept are very useful and helpful for fast and reliable formulation development. The overall concept was initially developed and programmed for seamless introduction into formulation R&D; the generally required initial dataset is not extensive and is usually satisfied with generally collected data for new or generic APIs. An introduction of F-CAD system into a routine formulation development work is beneficial as it speeds up time to market, cuts down the time and costs of extensive laboratory trials, and keeps acquired knowledge and experience on APIs, excipients, and their interactions in a readily-available compound library for further usage. It is important to keep in mind, that F-CAD can easily take care of more than one API, i.e. is an ideal tool for finding the optimal formulation in case of a combination drug.

Acknowledgements

The authors want to thank the different pharmaceutical companies, which allowed CINCAP GmbH to test F-CAD with real projects to establish a proof of concept (9). The authors apologize, that the nature and the exact formulations cannot be published due to secrecy agreements.

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His scientific interests are focused on massively-parallel computational models for a design of pharmaceutical formulations; discrete element models for design, understanding, and optimization of pharmaceutical processes and unit operations; interactive and process-oriented computer tools and simulators for advanced teaching and training of industrial unit operations.

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After his retirement. in 2006 from his position at the University of Basel he became involved in starting two spin-off companies ,i.e. the Institute for innovation in industrial pharmacy, IFIIP GmbH (www.ifiip.ch) and the Center for innovation in computer-aided pharmaceutics, CINCAP GmbH (www.cincap.ch). Recently he became a co-founder of AMIFICAS Inc., (www.amificas.com) i.e. of the American institute for innovative computer aided solutions, located in Florida, USA in order to make public the ideas of IFIIP GmbH and CINCAP GmbH in the United States.
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Hans Leuenberger received numerous scientific awards (see “awards gallery” of the homepage of IFIIP GmbH) and has published over 250 papers including over 10 patents. Over 90% of his former PhD students are working now in the pharmaceutical industry.

The Glatt stand at the Interpack 2011

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Excellence United is a strategic alliance of companies in the area of special machine engineering. All members are independent, medium-sized family companies and each one plays an acknowledged leading technical role in the respective segment of the market. This is expressed by the name "Excellence United". Together, the members of the alliance cover all of the stages of the production value-added chain for customers representing the pharmaceutical, medical technology and process industries, for whom Excellence United offers a unique network in terms of know-how, technology, service and Project Management – worldwide.

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Kick-off at the INTERPACK exhibition in Duesseldorf

Duesseldorf, May 12, 2011 – The pharmaceutical industry is currently undergoing a comprehensive transformation process. While health systems in established markets are subject to enormous pressure on costs, so-called "Pharmerging Markets" are experiencing impressive growth. This development faces pharmaceutical companies with a wealth of challenges while revealing numerous opportunities for suppliers of production technology. Driven by these developments, six leading technological companies representing special machine engineering established a strategic alliance in April 2011. The members of Excellence United are: Bausch+Ströbel, Fette Compacting, Glatt, Harro Höfliger, Uhlmann and Visiotec. Their joint offering is specifically aligned toward companies in the pharmaceuticals, medical technology and process industries, and covers all of the phases of the value-added chain: from laboratory equipment through manufacture of clinical samples and medication production to machines for end packaging. "Our aim is to take advantage of our joint offerings to significantly improve the productivity and efficiency of our customers' production, development and packaging processes", is how Siegfried Drost, CEO at Uhlmann and spokesperson of Excellence United, explains the alliance's objectives. The impulse for cooperation by these companies was given by the market: "Over the past few years, we've practically been passing each other the baton in numerous equipment projects involving operators pursuing a best-in-class approach. By bundling our competencies, we can now offer customers this performance from a single source. They in turn benefit from improved Interface Management, comprehensive documentation and on-site support."

The creation of Excellence United at Interpack 2011 was inaugurated by 2 events: first came a kick-off meeting on the evening before the exhibition started, for all stand staff members from the joining companies, and on May 12, 2011, an official press conference was held to inform about the new alliance.

All 6 companies represent technological leaders in their respective markets. Turnkey projects cover all stages of the value-added chain. International service network with more than 600 employees.

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Speaker Excellence United
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Continuously innovative

Glatt presents an all-new line-up of continuous processing machines at Interpack 2011

By Christian Schill, Glatt Binzen

The Glatt group welcomed many hundreds of international visitors to its booth and exhibits at Interpack 2011 in Duesseldorf, Germany between May 12th and May 18th.

The two-storey booth drew a crowd of visitors, who were not only enthusiastic about taking this excellent opportunity for some in-depth technical discussions and even some casual small-talk with the experts on the ground floor, but were also equally enthusiastic about grabbing some snacks and cocktails in Werner's Bar on the first floor.

Once again, Glatt's presence at Interpack underlined the group's continuing mission to deliver innovative technology to benefit the customer. One of the focuses this year was to show the possibilities offered in laboratory-scale continuous processing.

Although a great deal of noteworthy equipment was introduced at Interpack 2011 for the very first time, the following were considered particular highlights:

GCG 70

The GCG 70 is a machine for continuous High Shear Granulation, that is particularly suitable for the granulation of temperature sensitive materials which expand on exposure to moisture.

Products (in this case, dry solids) are brought into three-dimensional motion with mixing paddles and are moistened by spray nozzles. Stable granules are continuously formed and discharged through a GSF wet sieve further down the processing line. This ensures that the required grain size distribution and quality are constantly achieved.

GCG systems for the processing of between 10 and 120 kg of material per hour are available. Its space saving design makes it a perfect fit for premises where required space is a topic.

Thermo Fisher TSG

The Thermo Fisher TSG is a continuous twin-screw granulator for the manufacturing of particularly dense granules.

Thermo Fisher Scientific Inc. and Glatt GmbH announced a cooperative business agreement in the field of continuous twin-screw granulation and drying solutions for the pharmaceutical industry. This cooperation aims to satisfy specific customer demands with regards to continuous processing and particularly to granulation. Continuous processing could be one way to face the increasing pressures of cost in the global pharmaceutical industry.

GF 5 Insert for ProCell® Lab Systems

Glatt's new GF 5 insert brings continuous processing to the well-established ProCell® Lab systems. The solid raw material is continuously supplied. It moves in a circular motion through the processing chamber, which is divided into sections. These sections can be equipped with nozzles for spray granulation, agglomeration, encapsulation and coating. The final section is for drying the product before it leaves the unit.

The GF 5 can also be used as a continuous dryer, to dry moist raw material as it moves through the processing chamber from charging to discharge. The GF 5 is therefore perfect when placed further down the line from a continuous wet granulator.

GlattView® Control System

This new state-of-the-art control system embodies a uniquely intuitive graphical operating philosophy. It is designed to be as easy to use as possible and only be as complex as absolutely necessary, helping to make the control of every process clear and safe. All information required is displayed on a generous 19" touch screen at all times.

The GlattView® Control System is offered in two versions named "Mega" and "Eco". Due to its state-of-the-art technology, high operating reliability and fittingly ergonomical design, GlattView® ensures maximum flexibility for all current and future requirements.

The modular design of the multiple software options ensures that the GlattView Control System can be adapted to every conceivable requirement.

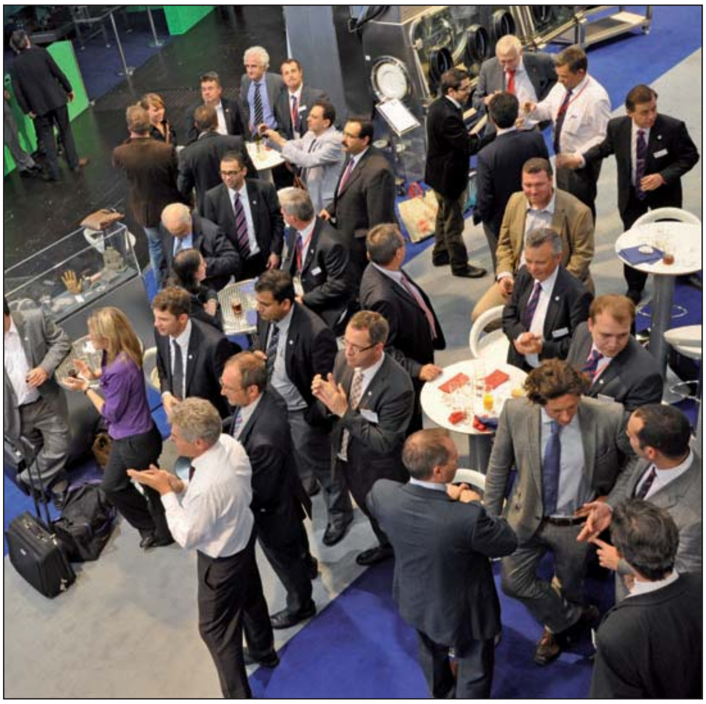
Laboratory Top Drive Granulator TDG

The versatile and mobile TDG is very convenient for the efficient mixing and granulating of small quantities of solids. Up to 5 litres per batch can be processed for research and development for the pharmaceutical and food industries. Great importance is attached to reliable up-scaling to production units.

The compact TDG Lab unit only requires an electrical power supply and a hot/cold water connection to work. Installation and operation are truly plug & play. The starting material, powder and binder liquid, are manually filled into the product bowl and, only a few minutes later, the granulation process is finished. The resulting granules can then be sent for further processing, such as sieving or drying.

Glatt Party at Interpack 2011

After the successful parties at the Glatt stand at Achema in 2009, Glatt again decided to host a stand party on the last evening of the Interpack exhibition with the theme " Duesseldorfer Night".
The party was held on the lower level of the stand and featured the "Duesseldorf Giants" cheerleaders, who demonstrated their impressive ability to thrill a large crowd of people.
On the catering side, local specialties from the Duesseldorf area were served, such as traditional "Alt" beer and appropriate food.
It was another highly entertaining evening, notable for good food, good wines and of course great conversations with our customers and friends.




Excellence United
The Community of Experts
Glatt

5th International Granulation Meeting

By Klaus Eichler, Glatt Binzen

More than 250 high-level attendees from the powder processing industry participated in this event, which was organized in Lausanne this time, at the end of June 2011, as a joint venture between Nestlé and the University of Sheffield. Besides a number of keynote plenary lectures, topical presentations were given in four lecture rooms simultaneously, not only focusing on granulation techniques, but also on filmcoating, pelletizing, process controls, modeling and simulation. Glatt was well-represented with an information booth, two filmcoating sessions chaired by Klaus Eichler and Michael Jacob, who additionally gave an oral presentation on process modeling. During his keynote lecture, Prof. Stefan Heinrich from the Technical University of Hamburg praised Glatt's scientific and financial engagement in furthering development of fluid bed technology. It was a mere coincidence that this year's TTC best poster prize was awarded to Sergiy Antonyuk and his coworkers for the poster "Coating of aerogel particles in spouted beds: Experimental study and DPM simulation", as the four-person TTC jury had already voted for this excellent poster prior to keynote lecture referred to above. The 2013 Granulation Meeting will again take place in Sheffield.
In the evening of the first day, a communal dinner on a large restaurant boat, cruising the eastern part of Lake Geneva, provided many opportunities for many individual discussions, both scientific and otherwise.

Coating of aerogel particles in spouted beds: Experimental study and DPM simulation

Sergiy Antonyuk[1], Stefan Heinrich[1], Irina Smirnova[2]

[1]Institute of Solids Process Engineering and Particle Technology,
[2]Institute of Thermal Separation Processes, Hamburg University of Technology, Hamburg, Germany

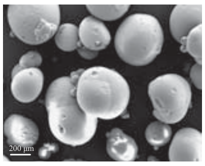
Objectives

The aerogels are nanoporous materials which show extremely low density, high surface area and excellent insulation properties.

Idea: production of spherical aerogel particles
→ a drug carrier with pH sensitive release

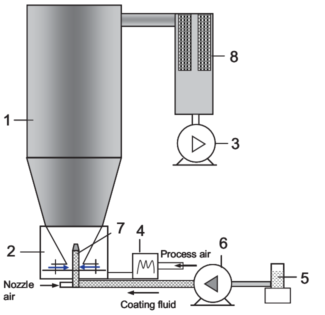
Aims of the study:

- Coating of spherical aerogel particles in the fluidized bed
- Description of particle and fluid dynamics in spouted bed apparatus during coating using Discrete Element Method coupled with CFD



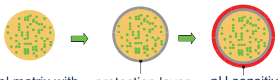
SEM of produced silica aerogel particles

Experimental: coating of aerogels

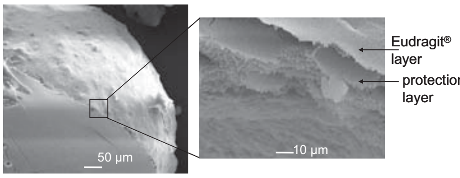


The experimental spouted bed apparatus for the coating of aerogels:

1 – cylindrical chamber
2 – prismatic fluidization chamber, with two horizontal gas inlets (slots) for adjustable gas supply
3 – blower
4 – 500 W heater
5 – vessel
6 – peristaltic pump
7 – two-component nozzle
8 – fabric filter



The droplets of Eudragit® solution can destroy particle surface of aerogel. To avert the breakage **the coating with two materials** was carried out. Firstly, PEG 2000 was sprayed in the apparatus forming a protection layer on the aerogel. After that the Eudragit® was injected.



Cross section area of an aerogel particle coated with two layers

Parameters of the coating experiments	PEG 2000	Eudragit® L
Process air mass flow in m³/h	25-40	25-40
Bed temperature in °C	45	21
Mass flow of the coating fluid in g/min	20	10
Temperature of the coating fluid in °C	95	25
Flow rate of the nozzle air in l/min	15-20	15-20
Temperature of the nozzle °C	80	30

Modelling of particle and fluid dynamics

Discrete particle model (DPM)

The motion of each particle *i* can completely be described using Newton's and Euler's laws:

Force balance for a primary particle

$$m_i \frac{d\vec{v}_i}{dt} = -V_i \nabla \bar{p} + \frac{V_i \beta_{g-p}}{1-\varepsilon}\left(\vec{u}_g - \vec{v}_i\right) + m_i \vec{g} + \sum_{j=1}^{m} \vec{F}_{c,j\,i}$$

Moment balance for a primary particle

$$I_i \frac{d\vec{\omega}_i}{dt} = \sum_{j=1}^{l} \vec{M}_{i,j}$$

Interphase momentum transfer coefficient $\beta_{g\text{-}p}$ was calculated by Ergun equation for dense regimes ($\varepsilon \le 0.8$) and by Wen&Yu for dilute regimes ($\varepsilon > 0.8$).

Contact forces between particles are calculated according to a viscoelastic contact model based on the Kelvin-Voigt law with a constant restitution coefficient (Cundall and Strack).

Normal and tangential contact forces

$$\vec{F}_{c,n}^{(ij)} = \left(k_{c,ij,n} \cdot s_{ij,n} + \eta_{ij,n} \cdot \dot{s}_{ij,n}\right) \cdot \vec{n}_{ij}$$

$$\vec{F}_{c,s}^{(ij)} = \min \begin{vmatrix} \left(k_{c,ij,s} \cdot s_{ij,s}^{a} + \eta_{ij,s} \cdot \dot{s}_{ij,s}\right) \cdot \vec{t}_{ij} \\ \left(\mu_{ij} \cdot F_{c,n}^{(ij)}\right) \cdot \vec{t}_{ij} \end{vmatrix}$$

The hydrodynamics of the gas phase: volume-averaged Navier-Stokes equations

$$\frac{\partial}{\partial t}\left(\varepsilon \rho_g\right) + \nabla\left(\varepsilon \rho_g \boldsymbol{u}_g\right) = 0$$

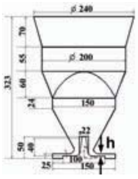
$$\frac{\partial}{\partial t}\left(\varepsilon \rho_g \mathbf{u}_g\right) + \nabla\left(\varepsilon \rho_g \mathbf{u}_g \mathbf{u}_g\right) = -\varepsilon \nabla p_g - \nabla\left(\varepsilon\, \boldsymbol{\tau}_g\right) - \mathbf{S}_p + \varepsilon \rho_g \mathbf{g}$$

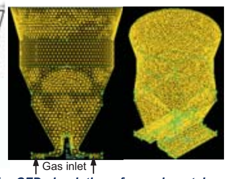
Simulation parameters and results

Mesh: 76,725 tet/hybrid cells, interval size: 0.008, minimum volume: 4 mm³

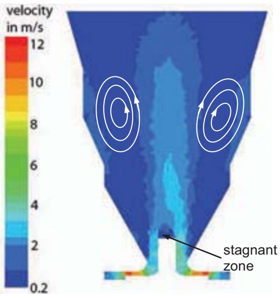
Air: Temperature: 25 °C, density: 1.18 kg/m³, viscosity: $15.7 \cdot 10^{-6}$ m²/s

Turbulence: k-ε model with the turbulence intensity of 5 %

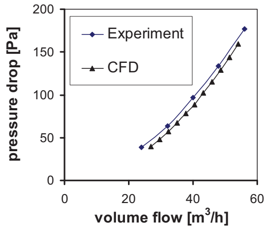




Fluidization chamber for CFD simulation of experimental spouted bed apparatus for the coating of aerogels

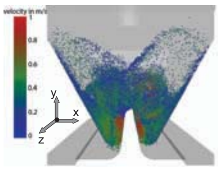


Plot of time-averaged fluid velocities in the empty apparatus at the inlet velocity of 2 m/s

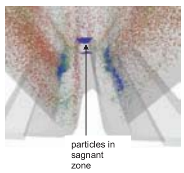


Comparison of calculated and measured pressure drop depending on the inlet gas volume flow

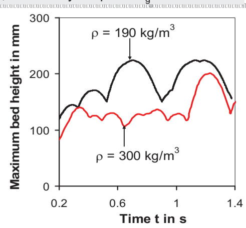
150,000 particles, d_p=0.8 mm (**uncoated**), d_p=0.82 mm (**coated**), ρ_p =190 kg/m³ (**uncoated**), ρ_p=300 kg/m³ (**coated**), restitution coefficient e=0.6 (**uncoated**), e=0.4 (**coated**), coulomb friction coefficient μ = 0.68, rolling friction coefficient 0.01, shear modulus of elasticity E=6.25 MPa, air velocity in spouts u_g=1.3 m/s



Instantaneous particle positions and velocity distributions inside apparatus

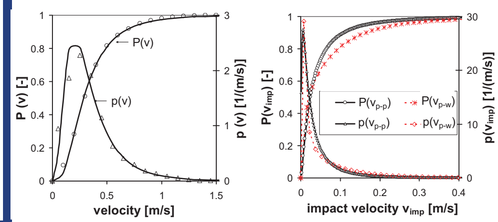


Particle deposition on the middle profile in the stagnant zone of the gas



The maximum bed height in the spout bed apparatus

Comparison of wet (300 kg/m³, e = 0.4) and dry (190 kg/m³, e = 0.6) aerogels



Distribution function P and its density p for:

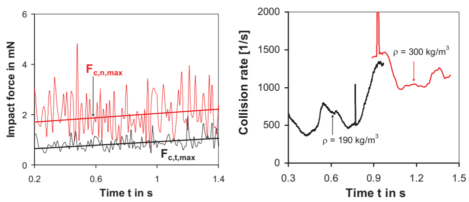
left: average absolute particle velocity

right: relative impact velocity in the spout bed apparatus

particle density of 300 kg/m³

p-p - particle-particle impacts

p-w - particle-wall impacts



left: Collision rate of the particles during the fluidization time

right: Maximal values of the normal and tangential impact forces (particle density of 300 kg/m³)

Conclusions

The process of coating silica aerogels with pH sensitive polymers was performed successfully in the experimental spouted bed apparatus.

To produce a closed Eudragit® layer and to avert the shrinking and breakage of the aerogel the particles can be coated with PEG 2000 as protection material.

The DPM simulations showed a high gas velocity in the bottom part of the apparatus and its gradual decrease over the apparatus.

The increase of particle mass and softening during coating leads to the decrease of the particle velocities and bed height and to the increase of the collisions rate.

No breakage of the aerogels was obtained because the impact forces acting in the fluidized bed are significantly smaller than the measured breakage force of aerogel particles

antonyuk@tuhh.de www.spe.tu-harburg.de Poster No. 11 5th International Granulation Workshop, Lausanne, 2011

High-quality granulates and pellets continuously manufactured in the ProCell

Full flexibility with the spouted bed

By Sebastian Pfütze, Glatt Ingenieurtechnik, Weimar

At the end of 2009, one of the world's largest spouted bed systems for granulation started at the Dresden-based contract manufacturer company IPC. A ProCell 250 supplied by Glatt Ingenieurtechnik GmbH enables a previously unachieved flexibility for agglomeration and spray granulation processes. Liquid and/or solid raw materials can be processed into granulates and pellets, or existing particles can be coated. Batch or continuous operation is possible.

Glatt Ingenieurtechnik GmbH is one of the leading suppliers of systems for continuous manufacturing of granulates and pellets using fluid bed and spouted bed technologies. Depending on the customer requirements, the scope of supply for granulation systems comprises of either the main equipment only, or the complete plant integration including the building design.

For IPC, Glatt Ingenieurtechnik delivered not only the technology and process equipment for the new manufacturing site, but engineered and implemented the entire building complex stretching over 4 floors.

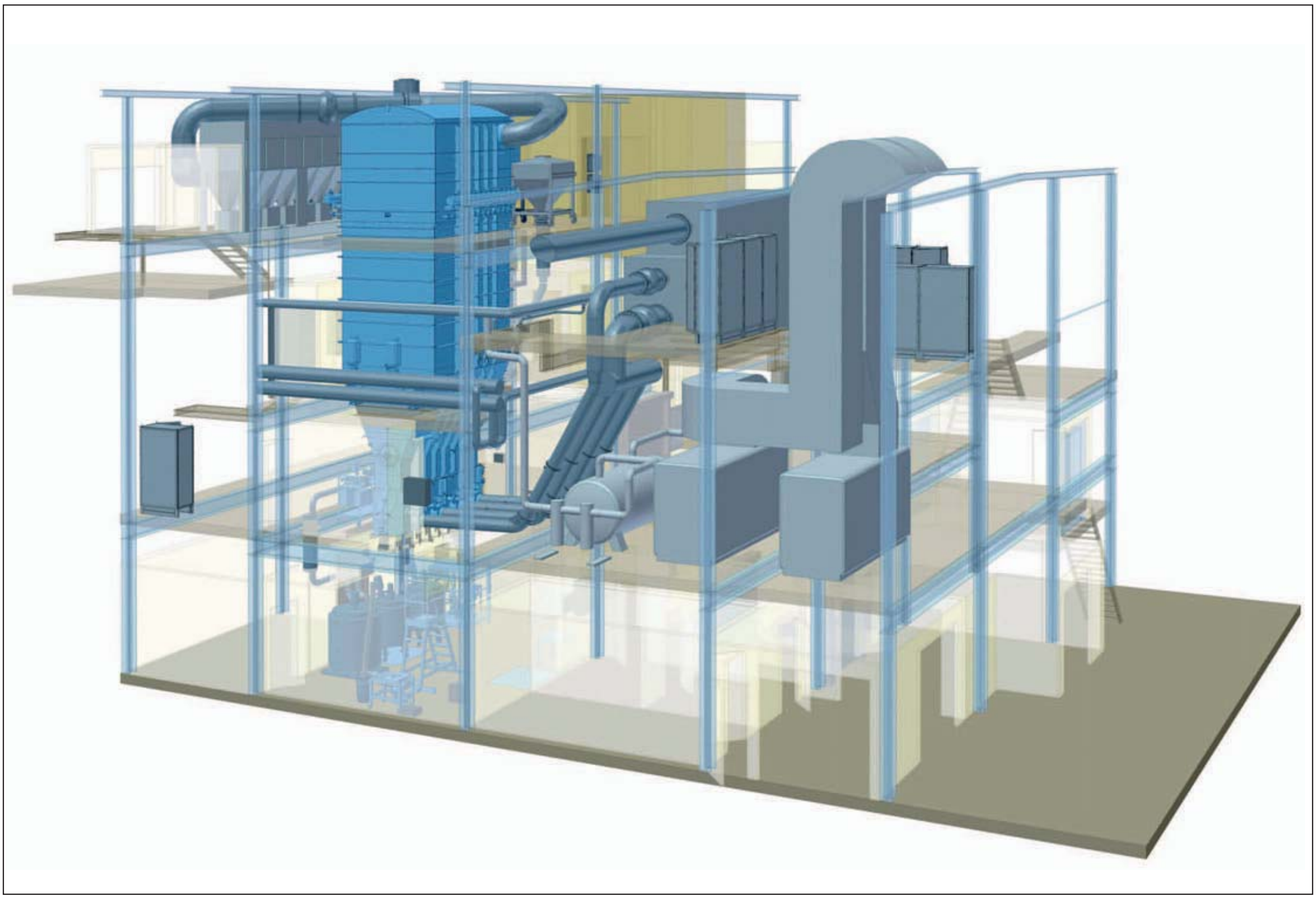
The solid raw materials, e.g. for powder agglomeration, are brought directly from the warehouse to level 1 of the plant. There, they are discharged into product containers on level 0 using a combined Big Bag and paper bag discharge station. After transporting the containers to level 3 by elevator, the containers are discharged via a docking station into the metering container of the gravimetric metering device.

Liquid ingredients are brought from the warehouse to level 0 where they are filled into a spray tank which can also be heated. From this tank, the liquids are directly sprayed into the ProCell 250 – and granulates are formed. The ProCell 250 stretches over 3 levels: Level 1: inlet air chambers and process chamber, level 2: expansion chamber with filter housing up to level 3: accessible clean gas chamber.

The granules leave the process chamber at level 1 and fall to level 0 by gravity. There, they can be cooled in a helical vibration conveyor if required. Then, the granules are pneumatically conveyed to a screen on level 2 where oversized and undersized particles are separated from the product.

Oversized particles are milled and pneumatically returned to the ProCell 250 process chamber together with undersized particles (screening-milling cycle). Screened product falls into a product silo at level 1. After the silo it discharges into a Big Bag filling station at level 0. Filled big bags are then transferred to the warehouse.

For a contract manufacturing plant flexibility and ease of cleaning are of great importance. The manufacturing and technical areas are strictly separated to protect the technical area against contamination by the product, therefore only the manufacturing area needs to be cleaned.




Level 0: Nozzle connections ProCell 250 (LH), spray tank and Big Bag filling station for product (RH)


Level 1: ProCell 250 Inlet air chambers and process chamber (LH), trolley with spray pumps (RH)

Level 3: Accessible clean gas chamber ProCell 250

In order to process products with a risk of dust explosion, the ProCell 250 is equipped with an explosion suppression system.

IPC - International Process Center - based in Dresden, is a certified manufacturing site for contract manufacturing of finished products for the food, feed and fine chemicals industries. For this reason, mainly advanced fluid bed processes with focus on granulation and coating are used.

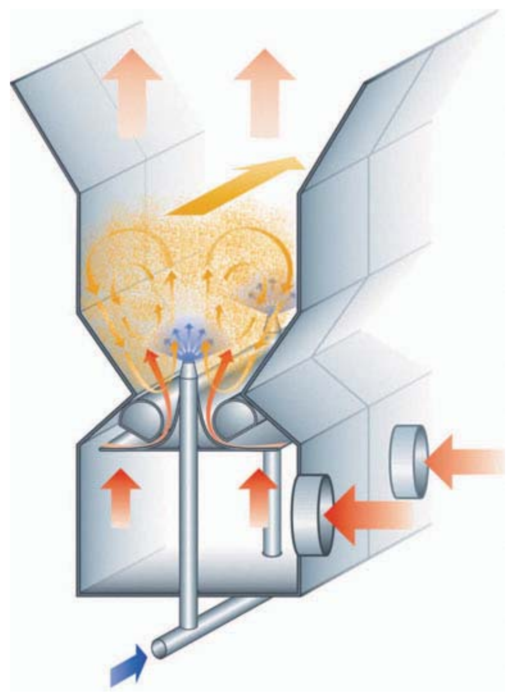
The production, with the ProCell 250 as the core equipment, is now the sixth plant on this site. Already in 2005, the first extension stage of one existing batch-type fluid bed system began. With entrepreneurial foresight, an existing warehouse was modified and extended. Also in this case, Glatt Ingenieurtechnik from Weimar was fully responsible for the planning and implementation of process equipment and building. Glatt Process Technologie GmbH in Binzen, the parent company of the Glatt Group, supplied a fluid bed Glatt Particle Coater Granulator GPCG 300.

This GPCG 300 was equipped with a larger filter and can be operated with an increased process gas quantity. This allows higher gas velocities for the process. The larger filter extends its service time and thus reduces the number of cleaning days. Hence this plant has the highest capacity out of the five batch-type fluid bed systems in Dresden. Three different process inserts allow different processes: fluid bed agglomeration with top spray nozzles, coating with the 32" Wurster and coating with the 46" Wurster.

In 2007, a ProCell 70 process insert was integrated into the GPCG 300 and the system extended by a screening-milling-cycle. Using this insert, for the first time IPC was able to offer the direct manufacturing of granules from liquid only by using the spray granulation processes. With the ProCell systems, IPC has the latest process technology from Glatt - the innovative spouted bed technology. (See box 1.)

All equipment components are selected with respect to easy cleaning, e.g. star feeders with quick-change star, or easily removable pneumatic conveyor pipes. The liquid pumps and the manifold for the spray nozzles are installed on trolleys that can be moved to the washing room. The ProCell 250 is equipped with a WIP system. The spray nozzles can remain in the plant during washing. The internal bag filter is washed by cleaning nozzles. Cleaning nozzles are also installed in the clean gas chamber.

When equipped with a bottom screen and thus operated as a fluid bed system, the tremendous process flexibility of the ProCell 250 can be further increased. The spray system is designed for spraying aqueous solutions and suspensions as well as molten substances. For spraying molten material, the spray system can be heated. Agglomeration and coating processes are possible by simultaneous metering of solid material and spraying of liquids. Process gas temperatures between 15°C and 200°C along with different process gas quantities also widen the application options of the plant.



In contrast to fluid bed technology, the process gas does not enter the process chamber across the chamber's whole cross section, but through two slots. A process gas jet emerges in the center of the process chamber. Glatt owns the patent for the integration of spray nozzles in spouted bed systems and uses it in ProCell systems. In priciple, all fluid bed processes are possible in the ProCell. However, the spouted bed technology offers additional advantages: Very fine products remain in the process due to the expansion of the process chamber. Very heavy products are able to be moved due to the high process gas velocity in the gap. The special geometry of the process chamber concentrates the product around the spray nozzle. This enables us to achieve equal spray rates with only 50% of the coating quantity of fluid bed systems. For continuous processes, this results in reducing the retention time by 50%.

Box 1: Spouted bed technology - ProCell systems

TECHNOLOGY TRAINING CENTER

Background

This workshop is conceived as a supplement to our theoretical filmcoating workshop, in order to explain and demonstrate potential effects on the desired functional filmcoating quality, caused by rheological variations of the raw materials or changes to their chemical properties.

Minor changes to the set-up of the pilot or production equipment for filmcoating may also be responsible for variations of the film quality: hardware parameters and software parameters both have equal effects, e.g. a different position of the spray nozzle, a change of the atomization air volume or the viscosity of a spray medium, can all easily alter the morphology of the film.

When using the bottom spray method, it is vital that the free area and configuration of the bottom screen, the distance of the partition to the screen and the process air volume be maintained for each specific product to be coated.

This workshop aims to explain and demonstrate potential quality deviations in-situ.

The coating processes will be performed, both as a batch and in continuous mode.

Workshop no. 169

Functional Filmcoating Practical Session

NEW

Topics

- **Potential interactions of excipients and core material during filmcoating**
  Dr. Iris Ziegler, Nycomed GmbH, Germany
- **The influence of ingredients rheology on filmcoating quality**
  Wolfgang Weisbrod, Evonik Röhm GmbH, Germany
- **Principles of batch and continuous particle filmcoating**
  Dr. Michael Jacob, Glatt Ingenieurtechnik Weimar, Germany
- **Clean-state inspection of test equipment to be used**
  Rheological verifications of materials to be used: Microscopy, IS0/ANSI methods etc.
- **Bottom spray filmcoating tests (batch)**
  Top-spray filmcoating tests (batch)
- **Hot melt coating tests (batch)**
  Cold lipid coating tests (batch)
- **Continuous filmcoating tests**
  Filmcoating quality assessment

Weimar, 27 - 29 September 2011

To register ▶ **www.ttc-binzen.de**

TECHNOLOGY TRAINING CENTER

Workshop no. 170

Pan Coating

Background

With growing international competition, many companies have to re-engineer their business to reach the target of improving yield, efficiency, market share and (if possible) profit.

On the other hand, universities and high schools are not equipped sufficiently to provide sound practical education.

We wish to fill the existing gap, having decades of experiences in building and using production equipment.

What makes us different from other institutions offering specialized training:

THE UNIQUE HANDS-ON-APPROACH

Who should attend

Operators and researchers from pharmaceutical and related industries where compliance to GMP standards, accuracy and reproducibility is imperatively required.

Speakers

Jochen Berger
Ecolab (Schweiz) GmbH, Switzerland

Thorsten Cech
BASF SE, Germany

Marcel Cimpan
Colorcon Ltd., UK

Wolfgang Dejan
Glatt AG, Switzerland

Philip Parmentier
Glatt AG, Switzerland

Christopher Scheer
Glatt AG, Switzerland

Wolfgang Weisbrod
Evonik AG, Germany

Topics

- **Aqueous film coating technologies in side vented coating pans**
- **Filmcoating process optimization**
- **GMP-conform cleaning procedures**
- **Practical demonstrations:**
  suspension preparation
  pellet or tablet coating
  nozzle maintenance
  scale-up
  trouble shooting
  factory tour
- **Important parameters in processing Eudragit polymers**
- **Thermodynamical considerations of the film coating process**
- **Excipients for filmcoating processes**

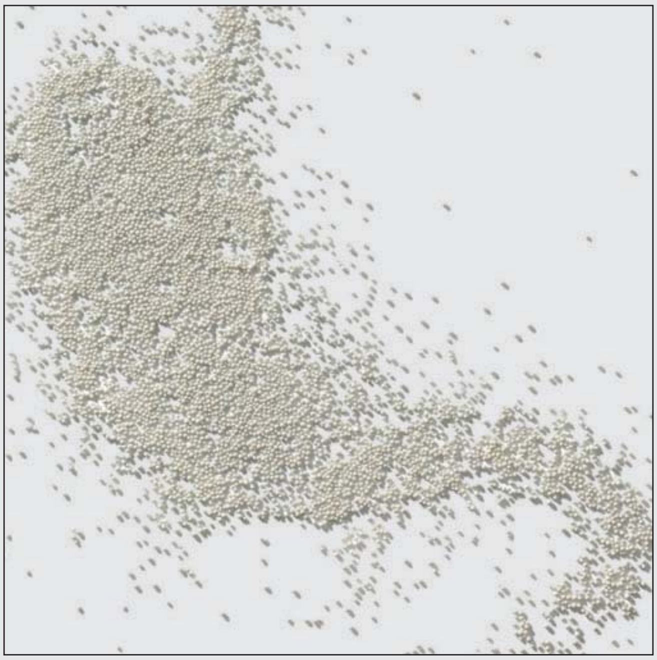
18-20 October 2011

To register ▶ **www.ttc-binzen.de**

TECHNOLOGY TRAINING CENTER

Workshop no. 172

Cellets



Background

Today oral dosage forms must fulfil various requirements, with terms such as multi-particular dosage forms and controlled release just a few of the common keywords in drug formulation. In addition customer compliance sets further benchmarks, shown in the rising number of oral dispersible tablet formulations for those with swallowing difficulties. Time to market the product, cost efficiency and robust manufacturing processes are last but not least further driving forces. Each and every aspect has to be considered in the development of new drug delivery systems demanding tailor-made and versatile excipients. Cellets, solely made of microcrystalline cellulose provide a neutral and extremely stable core material for drug layering processes.

The workshop strives to deliver a state-of-the-art overview on formulation of multiparticular dosage forms providing a more intense look during the demonstration session on the practical use of Cellets as starter cores.

Speakers

Alex Bowles
University of London, School of Pharmacy, UK

Dr. Frédéric Depypere
Gent University, Belgium

Gudrun Ding
IPC Process-Center GmbH & Co. KG, Germany

Dr. Frederic Gerber
Glatt Pharmaceutical Services, Germany

Dr. Caroline Kablitz
Novartis Animal Health, Switzerland

Fabian Klar
Heinrich-Heine-University, Duesseldorf, Germany

Dr. Gabrie Meesters
DSM Food Specialties, The Netherlands

Detlef Ortlieb
Glatt Pharmaceutical Services, Germany

Jan Ploen
Menarini - Von Heyden GmbH, Germany

Dr. Dirk Schmalz
Harke Pharma GmbH, Germany

Dr. Sven Stegemann
Capsugel, Belgium

PD Dr. Karl Gerhard Wagner
Böhringer Ingelheim, Germany

Topics

- **Multiparticular dosage forms - advantages of pellet formulations**
- **Application of Cellets in multiparticular dosage forms - a patent review**
- **Drug layering and coating of pellets**
- **Dry powder coating on coating quality**
- **Determining wear-resistence of coated particles during application**
- **Impact of compression on film-coated pellets**
- **Excipients for pellet processing**
- **Development of extended release pellet formulation containing a weakly basic drug**
- **Various pellet types as cores for dry coating for modified drug release formulations**
- **Application of multiparticulates for children's medicines**

22 - 23 November 2011

To register www.ttc-binzen.de