Innovative Glatt Fluid bed Pelletising Technologies

In multi-particulate systems the dosage of the drug substance is – in contrast to classic single-unit dosage forms like tablets – divided on a plurality of sub-units, consisting of thousands of spherical pellet particles with a diameter of typically 100 – 2000 µm. Although their manufacture and design is more complex in comparison to classic single-unit dosage forms, multi-particulate dosage forms offer a magnitude of different interesting options and advantages to accomplish unique product characteristics and in particular specific drug release patterns. In contrast to nondisintegrating monolithic single-unit forms which retain their structure in the digestive tract, the multiparticular preparations consist of numerous sub-units which disperse after administration. Each single sub-unit acts as an individual modified release entity. As a consequence of this property, the multiple-unit approach offers certain advantages for a modified
release dosage form over monolithic preparations like tablets:

- reduced variability of the gastric emptying
- reduced dependency on the nutrition state
- minimised risk of high local drug concentrations within the GI tract
- reduced risk of sudden dose dumping
- lower intra- and inter-individual variability
- controlled onset time of drug release
- delivery of the active ingredient to distal sites within the GI tract

With multiparticular pharmaceutical drugs an optimised pharmacokinetic behaviour can go together with good patient compliance. Many creative options in order to end up with intelligent, sophisticated and reliably acting pharmaceutical dosage forms are technically available. The question is: do we have feasible technologies in order to establish reproducible product and process quality? The described multiparticulate pellet units can be formulated to different drug application forms (fig. 1): the most conventional form is the capsule. Pellets may further be compressed to tablets – after disintegration of the tablet in the stomach the pellets are set free acting as multiparticulates. Pellets having a particle size < 500 µm can be applied as oral suspensions without providing a sandy mouthfeel. To achieve such small pellet sizes particular technologies providing micropellets are required – the extrusion technique is not applicable therefore (fig. 2). With classic fluid bed drug layering and coating technologies like the Wurster and the Rotor technology such pellet particle sizes are basically achievable taking into account that the Wurster process is limited to drug layering approaches; an optimised Rotor technology could lead to an even better performance than the existing one.
In addition to said existing and established pelletising technologies GLATT has developed new pelletising technologies (fig. 3) allowing new formulation options and product qualities. In particular, unique benefits and opportunities such as a small pellet size range of 100 – 500 µm, uniformity of particle size distribution, smooth particle surface, high density and high drug loading are achievable.

1. CPS™ Technology (Controlled Release Pelletising Technology)

CPS™ Technology is a direct pelletisation process resulting in matrix type pellets. Release characteristics of API from CPS™ pellets depend both on the pellet formulation and on the pelletising process. The CPS™ technology is an advanced fluid bed rotor technology allowing the preparation of matrix pellets with particular properties in a batch process; extremely low dosed and high potent drug can be formulated to CPS™ matrix pellets as well as high dosed APIs (fig. 2); the drug concentration can vary from < 1% up to 90%. Due to its modifications compared to the established GLATT Rotor system the CPS™ Technology works with a conical shaped rotating disc and additional devices ensuring a directed particle movement (fig. 4).

Inert starting beads are not required for the CPS™ Technology; typically, microcrystalline cellulose powder is used as a basic excipient; moreover, other functional excipients like polymers, disintegrants, solubilizers and the like can be part of the CPS™ formulations in combination with the API. The starting powder (blend) is wetted with the pelletising liquid until a defined stage of moisture will have been achieved; at this time, spherical pellets begin to form (fig. 5). The pelletising liquid can be water and / or organic solvents which may also contain functional compounds. As an option, dry powder may be fed into

Figure 1. Final drug application forms with pellets

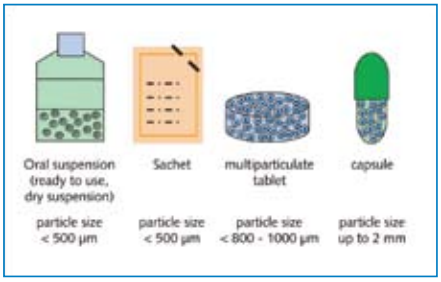
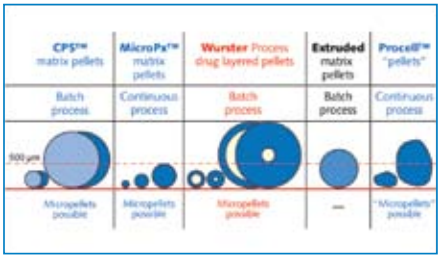


Figure 2. Product Characteristics with different pelletization technologies



the process. With the help of torque measurement at the CPS™ rotor the endpoint of the pelletisation can be defined. By means of a characteristic rolling particle movement and thereby the application of different forces, in particular of centrifugal forces on the arising pellet cores, a defined densification of the particles can be reached. Finally the pellets are dried in the CPS™ or in a classical fluid bed dryer configuration. Fig. 6 shows the characteristics of CPS™ pellets containing 75% of an API in comparison with the same pellet formulation manufactured by extrusion (fig. 7): the CPS™ pellets provide a higher density due to the particular spheronisation process; their surface is smoother than the one of the extruded pellets and therefore provides ideal prerequisites for coating applications. Outstanding product characteristics of CPS™ pellets:

- spherical and smooth pellet surfaces = ideal for coating applications
- high density / low porosity of pellets
- broad potency range for APIs
- low attrition and friability
- dust free surfaces
- mean particle size range: 100 – 1500 μm
- narrow particle size distribution (fig. 8)
- controlled drug release from the CPS matrix (fig. 9)

2. MicroPx™ Technology

The MicroPx™ Technology is a fluid bed agglomeration process resulting in matrix type pellets. Particle size could be rather small, e.g. < 400 μm together with a high drug loading of typically 95% (fig. 2). Functional pharmaceutical excipients, e.g. for bioavailability enhancement or controlled drug release can be integrated in the pellet matrix. The MicroPx™ Technology is a continuous fluid bed process: again, for the pelletisation, no starting cores are required. Typically, all formulation components like the API, pharmaceutical binder(s) and other functional ingredients are contained in a liquid which is fed into the MicroPx™ process via spray guns; the spraying liquid can be a solution, suspension, emulsion or the like. The design of the MicroPx™ technology is shown in fig. 10: in the pilot and the commercial scale a rectangular shaped processing chamber provides an ideal product flow. The fluidising air is led through a Konidur inlet air distribution plate into the processing area; by this means a directed air stream is provided allowing a directed product transport over the inlet air distribution plate towards the classifying unit. One or more spray guns are mounted in the air distribution plate. A set of cartridge filters will blow back dust into the processing area in a controlled manner. At the front of the processing chamber an on-line classification unit – a zig-zag sifter – is mounted in order to continuously discharge well-sized product from the continuous process and in order to keep product still being too small in size in the process. By adjustment of the classification air flow the particle size of the "good" product which must be discharged from the process is defined. As a number of channels – each of them having a number of edges – is used for the classification, a narrow particle size distribution is achieved (fig. 11). The direct pelletisation process starts with spraying the API containing liquid into the empty MicroPx™ fluid bed unit. Initially, powder is generated by spray drying; the powder is stepwise agglomerated to seeds. The online provided seeds are continuously layered with droplets from the bottom spray nozzles ending up in onion-like structured micropellets. The process is characterised by a permanently balanced ratio of spray drying and layering of already existing seeds. Well-sized pellets are continuously discharged out of the process through a rotary valve after classification by the zig-zag sifter. In order to allow spray drying besides the layering of existing pellets the product bed in the process must not be too high; this requirement is also true when the directed product flow towards the sifter should be put into effect.

Besides the classical fluid bed operating parameters such as inlet air volume, inlet air temperature, atomisation air pressure and liquid feed rate the classification air volume defining the particle size of the discharged product is characteristic for the MicroPx™ process. As a certain degree of spray drying is an important requirement for the performance of the continuous pelletisation process it is easily understandable that the product temperature is typically higher than in a Wurster layering or coating process where losses of product by spray drying must be absolutely avoided. Outstanding

Figure 3. Innovative GLATT pelletisation technologies

Figure 4. Rotor Technolog

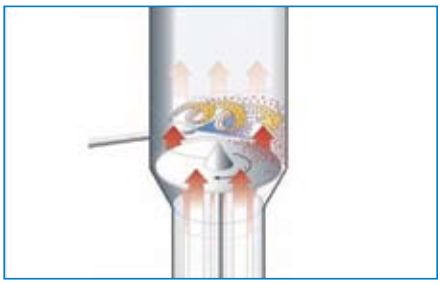


Figure 5. CPS™ Pelletising process in progress

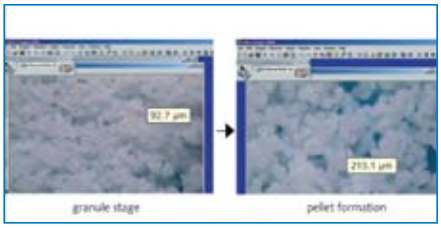


Figure 6. CPS™ Matrix Pellets

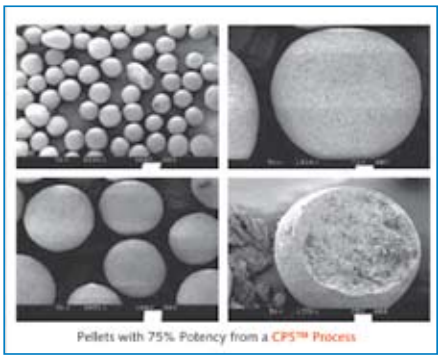


Figure 7. Pellets from an Extrusion / Spheronisation process

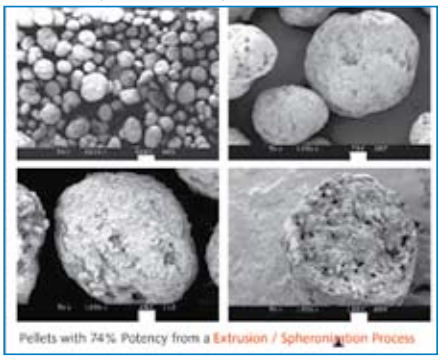
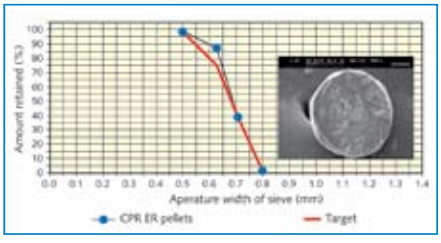


Figure 8. Particle size distribution of extended release CPS™ pellets



product characteristics of MicroPx™ pellets:

- spherical and smooth pellet surfaces = ideal for coating applications like taste masking, controlled release coating etc.
- high density / low porosity of pellets
- high drug loading: typically 95%
- low attrition and friability
- dust free surfaces
- mean particle size range: 100 – 500 µm
- narrow particle size distribution (e.g. > 90% between 100 – 300 µm without sieving)
- inclusion of bioavailability enhancers, controlled release polymers etc.

The MicroPx™ technology can ideally be applied when taste-masked micropellets must be manufactured – for the use in oral suspensions, sachets etc. For example, an extremely bitter tasting antibiotic should be formulated to an oral suspension to be given to children. The high dosed drug substance must be taste-masked in order to give a water based suspension which after the preparation must stay perfectly taste-masked for a 2 weeks period at room temperature. Nevertheless, the in vitro dissolution of the API from the taste masked form should be fast (> 75% after 15 min).

To fulfil these requirements the formulation of the API to micropellets using the MicroPx™ technology was decided. In the end, the taste-masked coated pellets should be smaller than

500 µm; fulfilling this requirement an unpleasant sandy mouthfeel is avoided.

Fig. 12 shows the formulation principle of the taste-masked micropellets: the API is included in the core which is seal coated before a final functional taste-masking coating is applied. Fig. 13 demonstrates the appearance of the uncoated micropellets and the narrow and reproducible particle size distribution thereof. Fig. 14 shows the cross-sectional view of the micropellets with the 2-layer coating. Fig. 15 presents the results of the taste-masking performance and the in vitro dissolution results: with the MicroPx™ pellet concept a perfect taste-masking could be achieved together with a very fast in vitro dissolution. Comparison of CPS™ Technology and MicroPx™ technology. The described innovative fluid bed technologies should be applied for different applications: MicroPx™ technology is the most feasible technology when particles with drug loading > 90 % must be provided in a particle size range of 100 – 400 µm; such small pellets are needed frequently for taste-masking applications but also for the compression of pellets into tablets. CPS™ is also able to provide a similar particle size range – typically lower API loads are intended and reached; a regular API load range is from 0,01 – 75%. As the densification can be well controlled by adjustment of the CPS™ processing parameters – in particular by the form and speed of the rotating disc – the CPS™ matrix pellets are most appropriate for a modified drug release from the matrix. Any functional coating can in addition be applied onto the CPS™ matrix pellets in order to achieve a particular in vitro dissolution profile. Both processes are appropriate to provide high valuable pharmaceutical products with unique properties. 3. ProCell™ Technology The Glatt ProCell™ Technology is a spouted-bed type pelletising process for the preparation of very high concentrated pellet-shaped particles; ideally, no additional excipients may be required for the formation of ProCell™ particles – in this case particles consisting of pure API are reached. Particles are fluidised in the ProCell™ spouted bed by a vertical process airflow: the process air enters the processing chamber through slots at the side and not through the usual bottom screen or inlet air distribution plate as in conventional fluid bed processing (fig. 16). The cross section of the processing chamber becomes significantly broader towards the top, resulting in a sharp decrease of the fluidising velocity of the process air. This effect provides a controlled flow pattern and circulation of the particles in the processing chamber.

Spray nozzles are usually arranged in the bottom spray position - right in between the two inlet air slots; in this position they spray at the point of the highest energy input inside the unit. The ProCell™ Technology is a direct granulation and pelletising process: again – like with the CPS™ and the MicroPx™ technology – no inert starting beads are required and either, solutions, suspensions, emulsions or the like, containing the API, can be processed. ProCell™ Technology performs in the most effective way when a melt of a

Figure 9. Effect of particle size distribution on the in vitro dissolutionof extended release CPS™ pellets (phosphate buffer pH 6.8, 37°C)

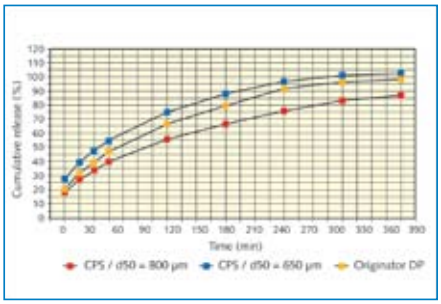


Figure 10. MicroPx™ Technology Pilot and Commcercial Scale

Figure 11. MicroPx™ Technology Zig-Zag-Sifter

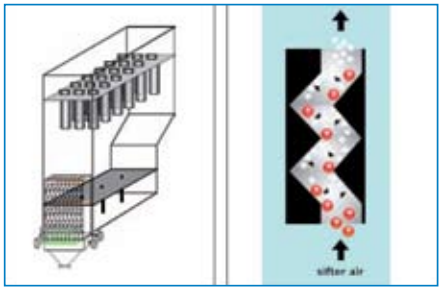


Figure 12. Taste masked MicroPx™ Pellets : Formulation Principle

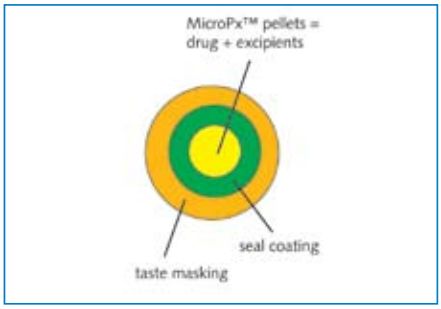


Figure 13. Appearance and particle size distribution of MicroPx™ Pellets

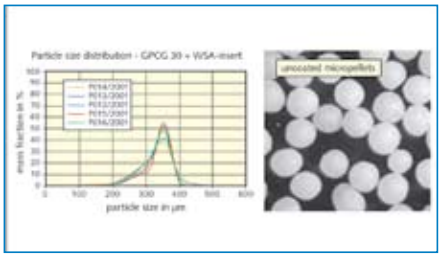


Figure 15. Taste masking performance and in vitro dissolution of taste-masked MicroPx™ pellets

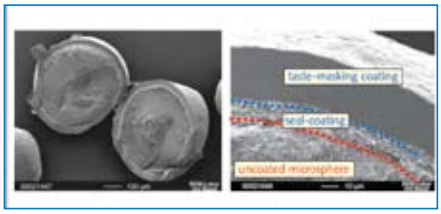


Figure16. ProCell™ Technology

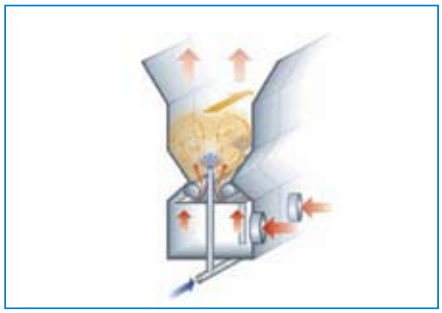


Figure 17. Ibuprofen DC grade 200 – 400 µm from ProCell™ Technology

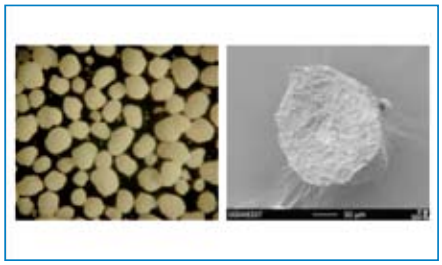


Figure 18. in vitro dissolution profile of Ibuprofen 200 mg tablets made with Ibuprofen DC grade from ProCell™ Technology

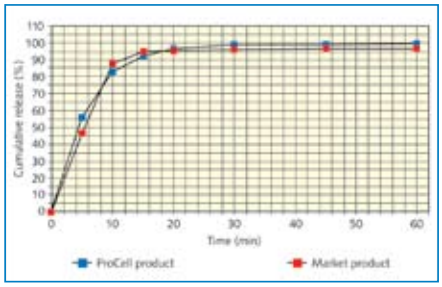
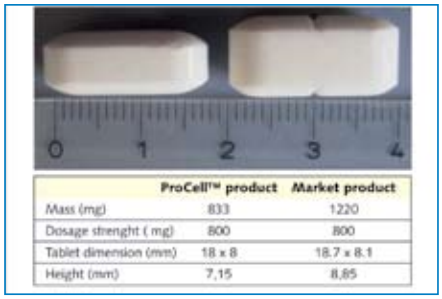


Figure 19. Ibuprofen modified release tablets made with ProCell™ granule



	ProCell™ product	Market product
Mass (mg)	833	1220
Dosage strenght (mg)	800	800
Tablet dimension (mm)	18 x 8	18.7 x 8.1
Height (mm)	7,15	8,85

material is processed, as in this case neither water nor organic solvents have to be evaporated; the formation of granules and pellets takes place by means of spray solidification and agglomeration. By this means, high through-puts and cost effective processes are possible. The continuously arising product quantities can be fractionated online by means of a zig-zag-sifter or offline by means of a sieving unit. In any case, separated material can be recirculated into the ongoing process; product losses are minimised in this way. Typically, ProCell™ particles may be spheronised less perfectly than with the CPS™ and the MicroPx™ technology Outstanding product characteristics of ProCell™ granules and pellets:

- very high drug load up to 100%
- mean particle size range from 50 – 1500 µm
- narrow particle size distribution

Figure 20. in vitro dissolution profiles of Ibuprofen modified release tablets (potency: 96%, ProCell™ granule) and a market product (potency: 66%)

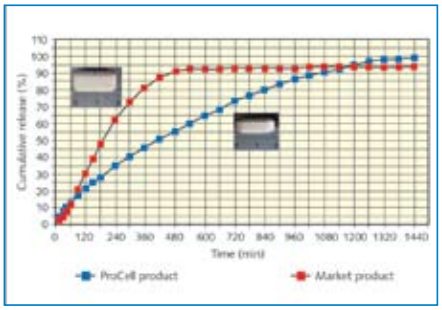


Figure 21. Innovative GLATT Technologies as Modules for Standard Fluid Bed Units: All-in-One Option

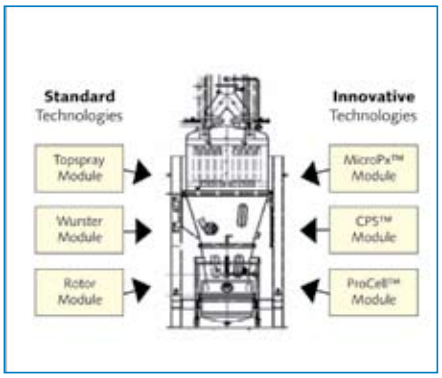
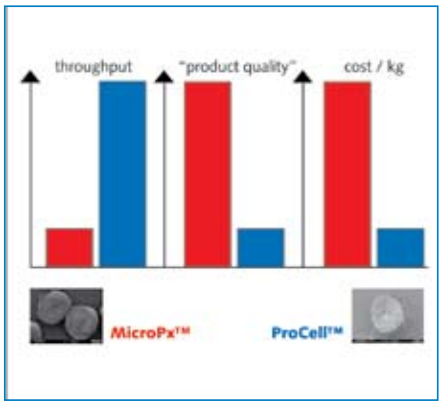


Figure 22. Product Quality / Throughput / Manufacturing cost with innovative GLATT continuous fluid bed technologies



- high density / low porosity of particles
- low attrition and friability
- particularily suitable for processing of products with inherent stickiness

Ibuprofen, a classic worldwide used API for pain killing has two negative drawbacks: during compression of conventionally produced granules very often sticking occures. Furthermore, Ibuprofen can cause a very unpleasant scratching in the throat during swallowing. In order to overcome the sticking problem during compression a Direct Compressible Ibuprofen grade was developed by Glatt applying the ProCell™ technology. The Ibuprofen DC grade was then compressed into 200 and 400 mg tablets. By this means - as a positive side effect - lower tablet weight and smaller tablet size can be achieved – and tablet manufacturers can eliminate the granulation step from their production when using the direct compressible Ibuprofen grade instead of standard Ibuprofen drug quality. The compaction properties of Ibuprofen DC grade were deeply investigated in commercial scale long time compaction studies ■

Dr. Norbert Pöllinger studied pharmacy at the University of Nürnberg-Erlangen, Germany, where he obtained his PhD in Pharmaceutical Technology in 1986. From 1987 until 1995 he worked at Bayer AG Leverkusen in the pharmaceutical development and headed the clinical supplies manufacturing group. In 1995 he joined Glatt GmbH where he is responsible for the Glatt Technology Center in Binzen, Germany.