CONTINUOUS GRANULATION TECHNOLOGY IN MANUFACTURING OF SOLID DOSAGE FORMS

ABSTRACT
Traditionally the manufacturing of pharmaceutical dosage forms has been a batch-wise process and continuous processes have limited applications in a pharmaceutical manufacturing plant. However, several factors are stimulating the pharmaceutical industry to investigate the opportunities offered by continuous processes. This production method provides an advantage towards quality assurance as the batch can be accepted or rejected. However, the increasing demand of pharmaceutical solid dosage forms necessitates the production of larger volumes of granules, requiring larger equipment. As all conventional machines for wet granulation (high shear and fluidised bed granulation) can only be operated in a batch-wise manner, several attempts have been made to develop continuous wet granulation techniques.

KEYWORDS Continuous granulation, wet granulation, fluidised bed granulation.
INTRODUCTION

Traditionally the manufacturing of pharmaceutical dosage forms has been a batch-wise process and continuous processes have limited applications in a pharmaceutical manufacturing plant. However, several factors are stimulating the pharmaceutical industry to investigate the opportunities offered by continuous processes.

Although in pharmaceutical manufacturing several individual operations are carried out in a continuous way (e.g. milling, tabletting and packaging) the production of granules is still, to a large extent, a batch-wise process. This production method provides an advantage towards quality assurance as the batch can be accepted or rejected. However, the increasing demand of pharmaceutical solid dosage forms necessitates the production of larger volumes of granules, requiring larger equipment. Hence it demands more capital investment, companies have to dedicate more resources to it (personnel and space) and it complicates the scale-up process. Therefore, continuous processing becomes an interesting process to the pharmaceutical industry because the same equipment can process smaller as well as large quantities by just extending the process time, thus eliminating any scale-up issues. As all conventional machines for wet granulation (high shear and fluidised bed granulation) can only be operated in a batch-wise manner, several attempts have been made to develop continuous wet granulation techniques.

Batch Granulation

In the pharmaceutical industry a granulation process is traditionally performed in a batch-wise manner, such as high-shear and fluid bed granulation. These processes have a simple set-up, whereby a certain amount of material is granulated, using equipment specifically developed for that amount of material.

The pre-weighed materials are charged into the granulation system, and after mixing and granulation, the granules are transferred to a drying system (Fig. 1).

![Figure 1: Material flow in a traditional batch granulation system](image-url)
The need for a continuous granulator

With the advent of US FDA’s process analytical technology (PAT) the industry is focusing on improving manufacturing efficiency and product quality. The goal of the PAT is to improve the product quality without validation risk and product delay.

Ironically batch processes have a number of problems, notably difficulties with scaling up and the difficulty in producing homogeneous processing conditions. The traditional methods of quality control have tended to concentrate on the end product such as testing the specification of a tablet, leading to considerable wastage when specification fails.

Continuous Granulation

Continuous granulation involves the use of a suitable device to continuously mix, wet mass and discharge the ingredients of a pharmaceutical formulation to produce granules suitable for drying and subsequent handling. Figure (2, 3) shows the schematically view of a continuous process with 3 different phases. The start up phase is the time necessary for the system to reach equilibrium. During the steady state phase, granules of a constant quality are produced. At the end of the process, the equilibrium is disturbed and a shut down phase is identified until all material is discharged from the granulator. The granules produced in the start up and shut down phase will have different characteristics from the granules produced in the steady state phase. It is important to keep the start up and shut down phases as short as possible to limit material loss.

![Figure 2: Material flow in a continuous granulation system.](image_url)
The advantages of continuous granulation are:

1. High production capacity
2. Reduction of cost and labour
3. Saving on space and time
4. Ease of automation
5. Avoiding scale up problems
6. Flexibility of batch size
7. Minimal wastage and fewer products at risk

Figure 3: Scheme of a continuous process
Heinen continuous fluid bed granulator

The most widespread continuous fluid bed agglomerators are horizontal moving bed granulators/driers (e.g. Heinen Drying Technologies, Glatt GF series, ) (Fig. 4), they are mainly used in the chemical, dairy and food industry (e.g. for the production of instant products) and these systems were not specifically designed for pharmaceutical use. Inside the granulation chamber several processes are accomplished as the chamber is divided into different functional sections which are not mechanically separated from each other. After dosing the raw materials into the fluid bed at the feed zone and initial heating of the powders, a liquid is sprayed on the fluidised particles to induce agglomeration. As the materials are further transported down the processing chamber, solid bridges between individual particles are formed during drying, consolidating the agglomerates. In the final section the material is cooled to allow further processing after discharge of the product from the fluid bed. The different functionalities along the chamber originate from the presence of the spray nozzles at the agglomeration zone and from the introduction of air having different velocities and temperatures in the different sections. Controlled movement of material (mainly plug flow) inside the granulation chamber is essential and is due to mechanically vibrating the processing chamber (resulting in a shallow powder bed height) or controlling the air flow using specific air distributor plates at the bottom of the fluid bed, thus ensuring that the fluidised particles are constantly transported from the inlet zone to the discharge area while continuously being agglomerated and dried A more stringent control of the agglomerate particle size is possible by recirculation of the fines into the fluidised bed, the fines being separated from the agglomerated material during discharge of the material, e.g. using a zigzag sifter separating fines by means of elutriation.

Figure 4: Heinen continuous fluid bed granulator
Glatt AGT continuous fluid bed granulator

Based on the same principle as the standard moving fluid bed Glatt developed the spouted bed systems (ProCell series). In these systems the air does not enter the fluid bed through a rectangular bottom sieve but through a longitudinal slit, a design claimed by the manufacturer capable of processing difficult-to-fluidise materials due to the high air speed at the point of entry.

Although the concept of continuous moving bed agglomerators can be used within the pharmaceutical industry, there are hardly any applications of them for the production of solid dosage forms, mainly because they are ideally suited for high-volume products: production capacities typically range from 20 kg up to several tons per hour. These systems are unable to operate at the lower capacities required during drug development when the limited availability of the drug might impose some restrictions. Hence, during the development stage another granulation technique is chosen, mainly batch-wise as these granulation processes can be downscaled to as low as 50 g per batch. When at a later stage higher volumes must be processed (full-scale production) the pharmaceutical industry often sticks to the agglomeration technique initially selected and does not go for a technology transfer, even if the required production capacity would be within the range of these moving bed granulators.

To be able to cover a range of production rates (from lab-scale to full-scale production) with the same continuous fluid bed technique, Glatt developed a fluid bed (AGTseries) where the material is confined to an enclosed space (similar to batch fluid bed processors), but able to continuously discharge agglomerated material through an outlet at the bottom of the screen (round-shaped) (Fig. 5).

A counter current air flow through the pipe positioned at the centre of the bottom plate ensures that only agglomerated particles are discharged. Only larger particles are able to overcome the air velocity, whereas the counter current airflow carries undersized particles back into the processing chamber until they are sufficiently agglomerated. This allows to manufacture an essentially dust-free product, the velocity of the counter airflow determining the particle size of the end product. This technique can be used for spray-granulation (spraying the raw material and building the agglomerates layer by layer) as well as conventional granulation (spraying a granulation liquid and possibly a binder onto individual particles in order to induce agglomeration). The latter method requires a powder dosing unit to continuously replace the solids being discharged from the fluid bed, in order to keep the solid/liquid ratio inside the processing chamber constant, an important parameter during a wet granulation process. This technique has a large dynamic range towards production rate as a lab-scale model for feasibility studies (throughput: 1 to 2 kg/h) as well as pilot-scale (50 kg/h) and full-scale production equipment is available.
Figure 5: Glatt AGT continuous fluid bed granulator

Spray-drier

Although conventional one-stage spray-drying can be considered a continuous process, the materials obtained using this technique are in most cases not suited for tableting purposes without further treatment. Often a product with poor flow properties is obtained, consisting of non-agglomerated single particles or—at the best—of loosely bound agglomerates. Therefore, if one wants to incorporate a spray-dryer into a fully continuous tablet production line, the spray drying technique has to be combined with another agglomeration technique in order to produce a free flowing product in agglomerated form. Multi-stage (two or three) systems, combining a spray-drier with an externally or internally mounted fluid bed, allow to manufacture products meeting these specifications. When a spray drier is linked to an external fluid bed the outlet temperature of the drying air is lowered to discharge a more moist product (compared to single-stage spray-drying) from the drying chamber into the fluid bed. The moist surfaces of the particles cause them to stick together, agglomerating the individual particles. The fluid bed, which is a in-line moving bed to allow continuous processing, can be used to further agglomerate the powders by spraying additional liquid onto the fluidised particles and/or to dry the agglomerates to the moisture content required for the down-stream processes.

Another design integrated the fluid bed inside the spray drier (Fig. 6) where the spray dried but still moist particles are collected in a fluid bed at the bottom of the spray chamber. Primary hot air is entering at the top and is used to dry the atomised particles, in addition a secondary air flow is introduced at the bottom of
the system to fluidise the agglomerate particles. Different agglomeration processes can be distinguished in this concept. The main agglomeration mechanism (forming the strongest granules) occurs in the fluidisation zone and relies on the moist surface of particles to coalesce or to intercept dry particles. This is the primary agglomeration mechanism as the residence time of particles in this zone is the longest. As smaller particles are propelled high into the chamber due to the fluidising air, there is the possibility of these fine particles colliding with each other (especially just above the fluid bed where they are still moist and particle density is the highest) or with atomised droplets, both enlargement phenomena. A third agglomeration mechanism (limited to the atomisation zone) occurs when individual droplets merge. Non-agglomerated material being exhausted from the spray-drying chamber is collected in the cyclone and these fines are recycled into the spray-drier. Size and characteristics of particles produced using this technique depend on parameters such as drying air temperature and spray characteristics, e.g. agglomerate size grows using a coarser spray and lower temperature as in that case particles dry slower and have a higher moisture content, enhancing agglomeration tendency. If required an additional external fluid bed can be added to the system (3-stage) in which the agglomerates are discharged for final drying to the required residual moisture content.

![Diagram]( attachment:Figure 6: Spray-drier with integrated fluid bed 1. atomization and drying of droplets, 2. Fluidisation: coalescence of moist granules + interception of dry particles by moist granules, 3. collision of smaller particles and atomised droplets, 4. exhaust of non-agglomerated material from drying chamber. }

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Extrusion granulator

Extrusion, the most studied continuous granulation technique for pharmaceutical applications, employs one (single) or two (twin) screws rotating inside a barrel to continuously transport, mix, and agglomerated wetted particles, the energy required for agglomeration provided by shear and/or material densification. Depending on the degree of densification inside the barrel the material discharged from the extruder can immediately be used (e.g. extrusion process run without die block) or requires an additional milling or chopping stage to reduce the dense extrudate to granules having an acceptable particle size range.

A major advantage of the extrusion technique seems the flexibility in output capacity, allowing development work as well as production on the same apparatus were able to cover a range in capacity from 5.6 to 18.5 kg/h using the same extruder, claimed that a specific type of planetary roller can process 0.5 kg as well as 100 kg, simply by extending the run time of the equipment (i.e. 3 min and 10 h, respectively). Obviously the small batch can only be processed if the granulation process reaches steady-state extremely fast after start-up.

Contrary to agglomeration techniques using a fluid bed, granulation by extrusion yields wet granules, hence these systems must be linked to a continuous drier (e.g. fluid bed, microwave).

The Bohle company developed an integrated granulating and drying system consisting of the planetary roller combined with a microwave drier (Fig7). To avoid the drying step, one could run a melt granulation process in the extruder using a molten binder (e.g. wax, polyethylene glycol) for particle agglomeration. Upon discharging the granules into an atmosphere of ambient temperature the binder solidifies to consolidate the granule. A similar process is possible in a fluid bed, spraying a molten binder onto the fluidised particles. Using the melt granulation process, it is essential to determine the effect of the binder on the dissolution properties of the granules.

Figure7: Planetary roller

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The quality of granules produced by extrusion depends on several parameters: extrusion temperature, design of the screws (i.e. the number of (back) mixing and densification zones), accuracy of powder and liquid dosing unit. Processes which can be classified in a similar category as extruders are ploughshare mixers and horizontal high-shear mixer, however the commercially available systems have too large production capacities to be useful within the pharmaceutical industry.

**Instant agglomerators**

A few systems rely on high-speed mechanical agitation to continuously mix powder and liquid, thus ensuring instant formation of agglomerates. A special feature characterizing these granulators is the very short residence time (seconds), as a consequence product hold-up (i.e. material being processed in the equipment at a given time) is limited, reducing waste at the end of the production cycle. These systems are capable of high production capacities, but (theoretically) also allow to process limited quantities of material due to the small product hold-up. However, if one is to use these systems to process small quantities it is essential to rigorously determine the equilibrium time as at start-up one possibly has to discard a too large amount of product before granules of constant quality are obtained.

The Nica M6 mixer/granulator (Fig. 8) uses a high-speed turbine to instantly mix the solids with the granulation liquid, whereas the Schugi Flexomix (Hosokawa) (Fig. 9) is equipped with blades rotating at high speed inside the processing chamber to generate sufficient mixing intensity and accomplish instant agglomeration. Similar to the granulation process by extrusion, the above-mentioned equipment produce wet granules, hence they must be linked to a continuous drying system (e.g. fluid bed). Due to the short residence time inside the mixing chamber the accuracy of the powder and liquid dosing units is essential to ensure a end-product of constant quality. Whereas the Nica mixer/granulator must be fed with a pre-blended powder, the Schugi Flexomix is also capable of mixing the powder components in the system and is already used in applications for bulk pharmaceuticals, although it has not specifically been designed for pharmaceutical purposes.

As these process should run without interruption, an essential feature needed is that the systems have to be self cleaning; no scale should form on e.g. the mixer wall or blades as this compacted material could break off and mix with other less-dense granules, creating a non-homogeneous end product. To avoid this, Schugi Flexomix is equipped with an interesting feature: the process chamber is fitted with external rollers flexing the elastomeric mixing chamber to prevent build-up of material on the inside.
Figure 8: Nica M6 Mixer/Granulator
Challenges in Implementation of Continuous Granulation

**Building requirements:** Production-scale single plots can weigh up to 10 tonnes. Therefore, a floor of appropriate strength must be prepared and the logistics of getting the equipment into the building considered, particularly if the equipment is not to be installed on the ground floor.

For the high shear granulator/fluid bed dryer combination, both a vertical and horizontal product flow are possible. Because the transfer of wet granules is a critical step, the high shear granulator being in an elevated position makes this easier and safer. Therefore, additional height (a platform or separate floor) is required.

Production-scale fluid beds can be several metres high; however, it is not necessary to install the whole unit in the production room. If it is built as a 'through the wall design,' all necessary technical installations can be positioned in a technical area. The upper part of the fluid bed tower can also be in a technical area above
the production room. Because of the complex material handling requirements of continuous production, these systems must be integrated into the building or, better still, the building must be tailored around the installation.

**Energy**

As energy consumption for drying is significantly higher than that generated by motors or vents, only the required drying energy amount is discussed. To evaporate 1 kg of water, 0.66 kWh of energy are required. The total amount of energy is both a function of the amount of liquid to be evaporated and the grade in which the equipment utilizes the energy supplied.

**Yield**

The yield of a process is particularly influenced by the time the process takes and formulation. Longer processes increase yield. The wetter the granulation process, the greater the material loss (as it sticks to the walls). A third important factor is the total surface area in contact with the product. These factors are not independent from each other. They are also influenced by product characteristics.

**Containment**

This is essential if processing toxic or very potent substances. In this case it is important to know if it is possible to achieve a closed material flow into and out of the equipment; if the equipment is tight; and if it can be cleaned automatically (including upstream and downstream connections), at least to a level where it can be opened without any danger. Closed material flow is possible for all processes shown. Even the very sensitive process of transferring wet granules via a wet mill from a high shear granulator into a fluid bed can be done closed. This is achieved by using modern split valve technology for contained docking to intermediate bulk containers. Other important factors affecting containment are how easily exhaust air filters can be changed without the risk of contamination; whether the equipment is operated continuously under negative pressure; and to what extent a sample can be contained.

**Organic solvents**

If processing with organic solvents, the equipment must be gastight. To eliminate the risk of an explosion it is necessary to either ensure that the mixture of organic vapours and oxygen is outside the explosion limits (which can sometimes be achieved in a spray granulation process) or that nitrogen is used as a process gas. If such processes are to rely entirely on the elimination of all potential spark sources, they must be carefully checked, case by case. Additionally, passive measures, such as a pressure shock design, suppression or venting, are always required except when using a single pot. This is because the risk of explosion exists only during the drying step, which is done under vacuum conditions.

If the exhaust gas contains organic vapours it must be cleaned. This can be done in a closed cycle by cooling, adsorption or catalytic burning. Again, the single pot, particularly if used without stripping gas, has an advantage: only the pure organic vapors must be treated.
Heat sensitive materials

To treat heat sensitive materials successfully, the temperatures and exposure time must be carefully controlled, as should the presence of moisture and oxygen. Single pot technology provides safe drying under vacuum, particularly if the granulation is done with organic solvents because the corresponding temperature is even lower. In a spray dryer, however, relatively high temperatures are involved, but only for a very short time. A batch fluid bed granulator can operate at higher air inlet temperatures while spraying and during the beginning of drying, reducing the inlet temperature afterwards to maintain a low product temperature. The nature of the product dictates which is the more appropriate treatment is.

Formulation limitations

High shear granulators are able to granulate all types of formulations. For single pot use, the behavior of all components exposed to microwave energy must be considered. Although this is not critical for most materials, it should be tested for new materials because of the small risk of an unexpected thermal runaway — the (microwave) absorption behavior relies on the moisture content or on the actual temperature.

Fluid beds inherently act as a classifier; that is, the particle size distribution (PSD) of all raw materials should be similar. Processing very fine powders can also be problematic because these particles tend to stay in the filter area. Sometimes this can be solved by introducing the spray liquid.

If a suspension is used to feed the spray dryer the suspended particles need to be smaller than 30 µm to allow a proper atomization. Tailor-made formulations containing, for example, a high amount of microcrystalline cellulose are needed to run an extrusion process. For poorly soluble actives in particular, the maximum drug load that can be achieved is limited. From a processing point of view, very soluble drugs can also cause many problems.

Granulation liquid

For the production of oral dosage forms, high shear granulators have almost replaced medium and low shear versions because their increased mechanical energy requires less granulation liquid to produce granules of similar properties. Also, smaller amounts of liquid added during granulation requires less evaporation during drying, resulting in a higher throughput and lower thermal stress for the active. The number largely depends on the nature of the formulation; whether the binder is added in a liquid or a solid form; and the granule characteristic required.

Fine particle amount

If the percentage of fine particles (<63 µm) is too large, flow problems, segregation and poor tablet formation become common issues. The relatively high amount of fines for the single pot process is typical of all types of vacuum drying. If seen as problematic, this can be reduced by adjusting the formulation.

Mean particle size

All processes allow the mean particle size to be controlled by varying some process parameters. The given limits can, in some cases, be extended for bespoke equipment.
Homogeneity

All technologies presented generally show no problems with product homogeneity. Mixing all components in a liquid stage followed by granule production in a one-step operation will give the best homogeneity level. The material produced in the continuous fluid bed granulator might, in rare cases, show some homogeneity problems, particularly if the material produced just after start-up and just before close down is examined separately and is not blended with the material produced in between.

Flow properties

Achieving free flowing materials are a major reason for including granulation. Therefore, only processes able to fulfill this requirement are of interest. The high shear granulation in general produces more dense and mechanically more stable granules. During vacuum drying, some of these granules are destroyed and a larger amount of fines is generated.

Bulk density

The bulk density required depends on the physical densities of the materials used, from the amount and type of binder liquid, the process parameters selected and the process by which the granulation is done.

Dissolution

How easily granules dissolve (instant properties) depends on their surface energy and structure. Granules produced with lower shear forces, show a more open porous structure, therefore, they have better instant properties, but are mechanically less stable.

CONCLUSION

There is a clear trend within the pharmaceutical industry towards increasing the production scale, fast running processes and increasing GMP and validation requirements, these factors have stressed the need to develop continuous process which has as few steps as possible and is able to work continuously without the need for expensive and time consuming scale-up trials. Continuous granulation, promises a new business model that will radically improve quality control, decrease scale up issues and cycle time and allow for faster release of new products.

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