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Continuous Granulation with a Twin-Screw Extruder

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A Introduction

1. Granulation

1.1 Definition and impact

Granules are by definition agglomerates made of primary particles. They are widely used in different industries. Different methods for the production of granules can be found for pharmaceutical purposes. On the one hand there are the wet granulation methods where solvents or binder solutions are used to agglomerate powders. Wet granulation methodologies are the fluid bed granulation, high shear granulation or the spray drying processes. On the other hand there are the dry granulation methods, using mechanical pressure for agglomeration, e.g. roller compaction and slugging. Meltable substances enable particle size enlargement for melt granulation processes, which can be performed e.g. in high shear mixers. In all these processes powder particles are enlarged up to granules with a particle size range from 0.1 to 2.0mm (Kristensen and Schaefer 1987).

Nowadays granules are usually used as intermediates for compression of tablets, the most often dosage form, or for filling of capsules. Originally granules were administered in sachets as a multiple unit dosage form.

Granules offer several advantages in comparison to pharmaceutical powders. In some cases they are as well necessary for the production of a solid dosage form: a prerequisite for the tablet production are good flowing properties which are improved with larger particle size (Rumpf 1958, Guerin et al. 1999). Thus free-flowing granules assure a good dosing accuracy during a tablet compression or capsule filling process (Gabaude et al. 2001). Another advantage is the increase in bulk density after an agglomeration step which enables a better control of drug content uniformity at low drug concentrations and avoids demixing or segregation processes (Faure et al. 2001). Furthermore granulation leads also to a reduction in dusting, an especially important fact for the production of high potent drugs (Augsburger and Vuppala 1997).

1.2 Batch versus continuous granulation processes

In the pharmaceutical industry the production of granules is still mostly based on a batch concept (Leuenberger 2001). Continuous process forms are considered to be feasible for only large volume productions and too inflexible for product changes which can occur daily (Vervaet and Remon 2005). However in the chemical and food industry continuous processes are well established for decades. They also offer several advantages for the pharmaceutical manufacturer. First of all costs can be reduced by replacing and combining process steps, e.g. to combine a blending and an agglomeration device in a continuous granulator. Thus equipment, space and staff can be saved. Scale-up challenges can be met by elongating the process time and increase the production capacity without a change of the equipment. Furthermore continuous processes are easier to automise (Lindberg 1988). Since process monitoring should accompany the whole production run, continuous processes are especially interesting for Process Analytical Technology (PAT) purposes. There are already tendencies to include PAT into the approval procedure for a drug, which may offer also a possibility to simplify the approval process.

1.3 Continuous granulation methods

A continuous granulator should be able to combine at least two process steps in one machine. Ideally powders are homogeneously blended and agglomerated during passage of a continuous granulator. Further process steps as drying can be added (Ghebre-Sellasie et al. 2002). So far there are some applications in the pharmaceutical field for the continuous production of granules. Vervaet and Remon (2005) gave an overview of the current process methodologies.

Roller compaction is a widely used method as it does not require an additional drying step (Kleinebudde 2004). This enables robust processes using small equipment. Agglomeration depends mainly on the compactibility of the used substances, thus high amounts of fines are often produced. This drawback can be met by using excipients with smaller particle sizes and thus reduce amount of fines in the final granules (Herting 2007).

Continuous fluid bed agglomeration, a wet granulation technique, is mainly used in the chemical and food industry. Although pharmaceutical applications are already described (Leuenberger 2001), they are still quite rare since primarily large volume products can be run on such a system.

Spray drying can be considered as a continuous granulation process, although materials obtained using this technique usually consist of non-agglomerated single particles or loosely bound agglomerates respectively showing poor flow properties. Therefore this process is combined with a following fluid bed agglomeration step leading to larger and free-flowing agglomerates. This results in a sophisticated process form, which is especially capable of large volume products.

In comparison high instant granulation seems to be more applicable for pharmaceutical wet granulation purposes. It affords a large volume production for different substances with a short residence time (Vervaet et al. 1994, Lindberg 1988).

In this context, twin-screw granulation can be seen as the latest process form for continuous wet granulation. Twin-screw extruders are supplied with powder by an additional dosing system. The powder is conveyed, agglomerated (after addition of a granulation liquid) and discharged at the end of the extruder. Extruders are available with counter- and co-rotating screws. They can be distinguished by their screw length and their screw diameter which is usually expressed with the dimensionless length to diameter (L/D) ratio. Furthermore an important attribute is the ratio of outside (OD) and inside diameter (ID) of the screws which describes the free volume that is offered for the material (Steiner 2003). The outer diameter refers the diameter of each screw for a twin-screw machine. The inside diameter is the OD less the depth of the flight.

2. Twin screw extruder

2.1 State of the art

Extruders were originally used in the plastics industry as well as in the food industry where they were applied for the continuous extrusion of pasta products. In both industries extruders are established since the first half of the 20th century (Mollan 2003). The market offers several types of extruders, e.g. screw extruders (single and twin-screw extruders), sieve or basket-type extruders, ring die press and ram extruders (Schmidt et al. 1997). For pharmaceutical purposes they are mainly used for extrusion-spheronisation purposes (Vervaet et al. 1995).

First applications of screw extruders for pharmaceutical granulations were made by Goodheart (1973) in the 1970s: a single-screw extruder was constructed for different applications. Extrudates of an antacid drug were produced via wet and hot melt extrusion. Granules were obtained after a following milling step. Gamlen and Eardley (1986) were one of the first to use the twin-screw extruder in the pharmaceutical field. The extruder was used in a fixed setup for the production of paracetamol extrudates. They evaluated the influence of the formulation composition and moisture on the quality of the resulting extrudates. Lindberg et al. (1988a, b) used a similar extruder setup and characterised the process for an effervescent granule formulation. The main focus was on determination of the mean residence time of the material. In a second step the influence of process parameters on intragranular porosity and liquid saturation of the extrudates was examined. The suitability of a twin-screw extruder and an instant granulator for continuous granulation was also demonstrated by Lindberg (1988). In this work the features and advantages of both machine types were described.

Schroeder and Steffens (2002) utilised a planetary roller extruder for agglomeration of hydrophobic materials: granule compactibility ought to be improved by increasing granule porosity. This was realised by means of a nitrogen injection device up to 10bar. Granule porosity could be slightly increased from 20% to approximately 23%. It was the first application of an extruder for processing of granules without a die plate. In the same year a complete continuous wet granulation process was patented by Ghebre-Sellasie et al. (2002). This patent includes also the use of a radio frequency or microwave based drying technique. In both studies a sieving step was used in which granules have to pass a milling device to obtain the desired particle size.

The first attempt to avoid milling of (dry or wet) granules was made by Keleb et al. (2002) by modifying the screw configuration. Firstly a standard screw configuration was applied, as it is common in the food industry for extrusion applications. An additional sieving step could be saved by running the extruder in a die less mode and by replacing discharge elements with conveying elements of a higher pitch. A comparison of the twin screw extruder with a high shear mixer for the granulation of lactose showed the higher effectiveness (Keleb et al. 2004a, b): the twin-screw extruder produced granules with higher yield values, and same granule quality was obtained although different lactose grades were used. Van Melkebeke et al. (2006) used this modified screw configuration also for melt granulation purposes: polyethylene glycols as binders were used for the development of a veterinary drinking water formulation with immediate drug release. A current study dealt with the validation of a continuous granulation process (Van Melkebeke et al. 2008). The effect of modifying the screw configuration by changing the number and configuration of mixing zones was investigated. The process was identified as robust since mixing efficiency remained good irrespective of the applied modification.

2.2 Screw configuration

2.2.1 Impact

Usually the screws of a twin-screw extruder are built up modularly. A series of unit operations can ideally be combined in a downstream process. This is already done in the plastics industry where it is a common approach to change and vary the screw configuration until the desired product is reached. A unit operation is realised by a discrete element or a combination of screw elements, e.g. feeding-, conveying-, mixing- or retaining functions are possible. The classical twin-screw element shapes are well described in literature. Erdmenger (1949, 1951) introduced the conveying and kneading elements for intermeshing co- and counter rotating twin-screw extruders. Up to now several other element types were introduced, which are mainly used in the plastics industry. Kohlgrüber (2007) made an overview of the available patents concerning screw element geometry. Screw elements are primarily defined by their number of flights. In this work always two flighted elements were used, i.e. conveying- and kneading elements, as classical screw elements, and the newer combing mixer elements were applied (Fig. 1-3, all by courtesy of Leistritz Extrusionstechnik GmbH).

2.2.2 Conveying elements

Classical conveying or forwarding elements are always inserted at cylinder openings, e.g. at barrel holes to convey material away from the feed opening or to discharge processed material at the end of the extruder (Thiele 2003). They also serve as drivers to provide forwarding pressure to supply material into kneading and mixing elements. Additionally they assure the self centering of the two screws in the extruder barrels. They can be distinguished by their number of flights, element length and the element pitch. Conveying properties improve with increasing element pitch since more volume is offered for the material and thus more material is conveyed with each revolution. For extrusion purposes the ability to pressurise the die improves with decreasing element pitch. The market also offers reverse flighted conveying elements which are used for retaining purposes. This type was not applied in the current work. In Fig. 1 two examples of the tested conveying elements are shown. The difference is the element pitch: on the left hand side a 20mm pitch element is shown which is typically used to pressurise the die. A standard conveying element with 40mm pitch is shown on the right hand side. It is usually employed for feeding and conveying tasks.

Fig. 1 Conveying elements of 90mm length with 20mm element pitch (left) and 40mm pitch (right)

2.2.3 Kneading elements

Kneading elements or kneading blocks, the second classical element type, are usually used when material has to be sheared and dispersively mixed (see chapter A3.3). They are built up out of several kneading discs which determine the element length. These kneading discs are staggered with a different angle which is described by the advance angle. Fig. 2 shows three different types of 30mm long kneading blocks with advance angles of 90°, 60° and 30°. The advance angle also determines the conveying ability of the element ranging from forwarding (30°, 60°) and neutral (90°) to reversing (30°reverse) character. Neutral elements (90°) push material neither forward nor backward (Thiele 2003). Irrespective of the reverse flighted element ability for mixing and shearing of the material increases with higher advance angle. Reverse flighted kneading blocks have a retaining character and are usually utilised when large mechanical stress has to be exerted onto the material.

Fig. 2 Kneading blocks of 30mm length with 90°, 60° and 30° advance angle (from left to right)

2.2.4 Combing mixer elements

Combing mixer elements meet the challenge of conveying and mixing simultaneously. Basically they are conveying elements with longitudinal slots. These slots provide more space for distributive mixing (see A3.2) without or nearly no loss in forwarding properties. They are differing, similar to the conveying elements, in their number of flight, length and element pitch. Fig. 3 shows combing mixer elements with a 15mm pitch and a length of 60mm.

Fig. 3 Combing mixer elements of 60mm length with 15mm element pitch