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International Journal of Pharmaceutics 278 (2004) 165–172

international journal of pharmaceutics

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Milling of agglomerates in an impact mill

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Received 3 January 2004; received in revised form 8 March 2004; accepted 9 March 2004

Abstract

Milling of agglomerates is one of the common unit operations during preparation of oral dosage forms like capsules and tablets. In literature the breakage of granules is mostly determined after single impact at an ideally formed granule or of single particles. In this paper the breakage behavior of agglomerates after milling with multiple impacts has been studied. It investigates the effects of the formulation and the influences of the mill settings. With respect to the formulation it has been found that both the size of the particles before granulation and the amount of binder used determine the breakage behavior. Both parameters have an influence on the strength of the granule to be milled, where initial particle size has the largest effect. A relation has been found between the strength of granules and the degree of size reduction. Regarding the mill settings, there are no mill parameters which influence the formation of fines independently. Formation of fines is always the result of the total degree of size reduction. It is not possible to achieve a large degree of size reduction without intensive fines formation. The results indicate that it is possible to achieve every desired average particle size. However, when formation of dust has to be reduced, multiple milling steps with separation of in-size particles is necessary.

Keywords: Agglomerates; Milling; Impact; Particle size; Size reduction

1. Introduction

Production of tablets and capsules in pharmaceutical and food industries includes a sequence of unit operations like mixing of main compounds, granulation, size reduction, mixing with glidant and lubricant and finally tabletting or encapsulation. The mixing/granulation step is necessary to guarantee a sufficiently homogeneous distribution of a small amount of active compound in the powder mixture. Size reduction is performed to create a particle size distribution that guarantees good tablet production or capsule filling. While size reduction of single materials has been the topic of interest in many papers (Narayanan, 1986; Vogel and Peukert, 2002; Mishra and Thornton, 2001; Airaksinen et al., 2000), granulate size reduction has received much less attention. The granulation process does not always give exactly equal products and size reduction is known to be sensitive to alterations in properties of feed materials. The physical properties of granules are related to the inter particle cohesion, the size of the particles, the principle of particle size enlargement and the process conditions used (Mishra

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doi:10.1016/j.ijpharm.2004.03.006

and Thornton, 2001; Airaksinen et al., 2000). This sometimes leads to a product with unpredictable properties during dosage form production. For this reason, there is a need for a deeper understanding of granule size reduction. In literature, different studies of the breakage of granules are reported (Narayanan, 1986; Vogel and Peukert, 2002; Mishra and Thornton, 2001; Airaksinen et al., 2000). This study is to evaluate whether theories and rules that are known in situations where size reduction occurs of single materials and model granulates after single impact are applicable in granulate size reduction by multiple impact.

2. Materials and methods

The formulations in this study are standard formulations for production of oral dosage forms and consist of lactose monohydrate (DMV, Veghel, The Netherlands) and corn starch (National Starch and Chemical Company, Bridgewater, NJ, USA) using a hydroxypropylcellulose (Klucel EF, Hercules, Düsseldorf, Germany) mucilage as a binder.

In the first set of experiments the granulates were prepared with different types of lactose and different amounts of HPC using a Gral 25 high shear granulator (Collette, Wommelgem, Belgium) at 5 kg scale with the compositions as depicted in Table 1. Table 2 lists volume based mean particle sizes of the starting materials.

Table 1
Composition of granulates

Ingredient	Amount (% by weight)
Hydroxypropylcellulose	2 or 3
Corn starch	10
Lactose (100, 200 or 450 M)	to 100

Table 2
Properties of the starting materials

Ingredient	$D_{v,0.5}$ (μm)
Corn starch	14
Lactose 100 M	149
Lactose 200 M	75
Lactose 450 M	38

The rotational rate of the impeller was 130 rpm and that of the chopper 1500 rpm, while the granulation time was 15 min. After granulation the granules were dried at 40 °C under reduced pressure in an Elbanton vacuum stove (Kerkdriel, The Netherlands). The granules were separated into defined size fractions with a Mogensen K7 (Mogensen GmbH & Co., Wedel, Germany) vibrating sieve. The fraction containing granules with a particle size between 1000 and 1600 μm was used for further experiments. Aliquots of about 100 g were milled with a Comil 193 AS high shear conical screen mill (Quadro, Waterloo, Ont., Canada) using a screen with standard round bores with a diameter of 0.61 mm, while the rotational rate of the impeller was 3000 rpm. Samples were taken during continuous feeding of the mill in order to be able to study the milling behavior under steady-state conditions. The particle size distributions of the to-be-milled and the milled agglomerates were determined with a Sympatec Helos Laser Diffraction Particle Size Analyzer (Clausthal-Zellerfeld, Germany) using the Gradis feeding system and Windox version 3.4 software for calculation of the data.

In the second set of experiments the mill settings were varied while the composition of the granulate stayed equal, i.e. 88% lactose monohydrate, 10% corn starch and 2% hydroxypropylcellulose (HPC). This batch was prepared in a Vactron 75 high shear granulator (Collette, Wommelgem, Belgium) at 25 kg scale. The rotational rate of the impeller was 110 rpm and that of the chopper was 1500 rpm. Drying and fractionation has been performed as described earlier in this section. Three different size fractions were used for further testing (Table 3, data based on supplier information). Mill settings that were varied were; impeller speed, screen size and screen type.

Table 3
Mean granules sizes of granules used for testing the effects of mill settings (measured by laser diffraction)

Mogensen sieve sizes (mm)	$D_{v,0.5}$ of granulate (μm)	$D_{v,0.1}$ of granulate (μm)	$D_{v,0.9}$ of granulate (μm)
3.15–2.00	1713	1234	2116
2.00–1.60	1295	843	1638
1.60–1.00	854	551	1166

3. Results and discussion

3.1. Influence of the formulation on breakage behavior at constant mill settings

In order to be able to quantify the degree of milling, the size reduction ratio (SRR) has been introduced:

$$\mathrm{SRR} = \frac{D_{\mathrm{v},0.5\ (\mathrm{b})}}{D_{\mathrm{v},0.5\ (\mathrm{a})}} \qquad (1)$$

where $D_{\mathrm{v},0.5\ (\mathrm{b})}$ is the median of the granulate size distribution (volume based) of the sample before milling and $D_{\mathrm{v},0.5\ (\mathrm{a})}$ is the median of the granulate size distribution (volume based) of the sample after milling.

Fig. 1 gives the degrees of size reduction for the different formulations.

The results show a decrease in SRR when the lactose particles are smaller in size. Furthermore, the size reduction ratio tends to decrease when the amount of HPC increases in the formulation. It is possible to regard an agglomerate as a cluster of particles bonded together by HPC bridges. Pietsch (1991) stated that the most important characteristic of an agglomerate is its strength which is mainly determined by the binding mechanism. When it is assumed that these bonds are weak compared with the strengths of the original particles, fracture of the agglomerates will predominantly take place via these HPC bridges.

The assumption that HPC bridges determine the strengths of the granules makes it possible to calculate the granule strength using the equation by Rumpf (1970). This equation correlates the strengths of granules with the size of the primary particles in the granules and the strength of adhesion between the particles:

$$\sigma = \frac{1-\varepsilon}{\pi} \times k \times \frac{F\mathrm{a}}{D^2_{\mathrm{v}.0.5}} \qquad (2)$$

where σ is the strength of granule; ε is the porosity; k is the coordination number; F_a is the force of adhesion between particles and $D_{\mathrm{v},0.5}$ is the median particle size of starting material.

This relation makes it possible to estimate the relative alterations in granule strength as an effect of the formulation, when making the following assumptions:

- porosity and coordination number are independent of formulation;
- force of adhesion is entirely determined by the surface coverage of the particles in the granules by the HPC binder.

The surface coverage of the particles in the granules basically determines the ratio of the mass fraction HPC in the formation to the specific surface area of the particles. The relative strength of the granules can be calculated using:

$$\frac{\sigma}{\sigma_\mathrm{ref}} = \left(\frac{D_{\mathrm{v},0.5,\mathrm{ref}}}{D_{\mathrm{v},0.5}}\right)^2 \frac{\theta}{\theta_\mathrm{ref}} \qquad (3)$$

where σ_ref is the strength of reference granule; $D_{\mathrm{v},0.5,\mathrm{ref}}$ is the median particle size of reference starting material; θ is the surface coverage by binder and

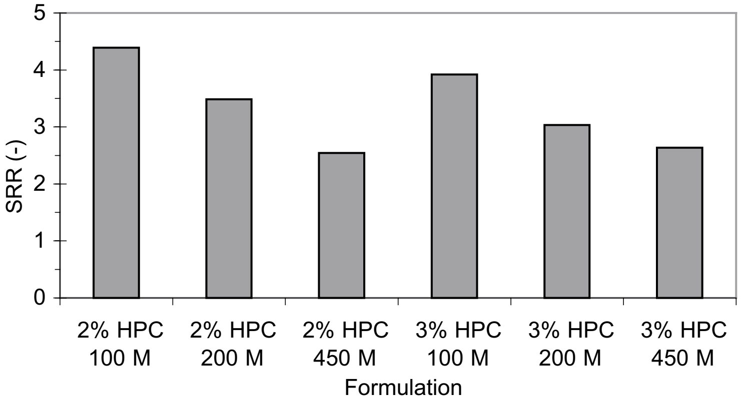

Fig. 1. The size reduction ratio of different formulations milled under equal conditions (impeller rate 3000 rpm and a 0.61 mm screen with spherical bores).

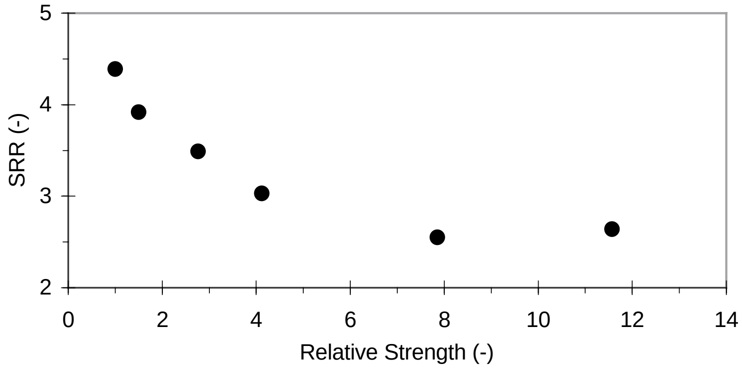

Fig. 2. Size reduction ratio as a function of the relative granule strength (milling conditions as in Fig. 1, see text for calculation of the relative strength).

θ_{ref} is the surface coverage by binder of reference formulation.

Here, the formulation containing lactose monohydrate 100 M and 2% of HPC acted as reference and the strength of these granules has arbitrarily been set at 1. Fig. 2 gives the size reduction ratio as a function of the relative strength of the granules made containing either lactose 100, 200 or 450 M and different binder contents.

From this figure it easy to see that the degree of size reduction (under constant milling conditions) is directly correlated with the strengths of the granules. The figure also shows that the size reduction ratio reaches a constant (minimum) level when granules are strong. This is due to the fact that the milled granules have to be of a certain size in order to be able to leave the mill. The degree of milling will always be such that the particles are fine enough to be able to pass the screen. This size will be independent of the granule strength. When particles are weaker, then the SRR is higher (Fig. 2). In this situation, it is apparently not the size of the screen that determines the particle size distribution of the milled material, but the strength of the agglomerates. As an effect, the degree of size reduction of weak granules is larger than the size reduction that is necessary for granules to leave the screen. The conclusion from this discussion is that the screen size finally determines the maximum particle size of the milled material, but when the granules of the feeding material are weak, than it will be the impact that determines the degree of size reduction.

The assumption that granule fracture is predominantly adhesive fracture (i.e. the mother particles remain highly intact) makes it possible to correlate the observations in Fig. 1 with Subero and Ghadiri's (2001) theory of crack branching. An impact on an agglomerate leads to a crack in it. The large amounts of flaws in agglomerates consisting of small initial particles (lactose 450 M) make it possible for the initial cracks to propagate through the entire agglomerate after impact. This results in a number of relative large fragments. In contrast, when there are less flaws (lactose 200 M), then less crack propagation via the initial cracks is possible (assumed only adhesive crack at HPC bridges, Section 3.1). The particle fails at the place of impact. Here, the mother particle remains highly intact and very fine debris is formed (Subero and Ghadiri, 2001). As a consequence, the remaining mother particle has to undergo several impacts until its size is sufficiently reduced to leave the mill. The final effect is that granules consisting of larger particles show a larger degree of size reduction.

In addition to the degree of size reduction, the fines formation can be a relevant parameter too, as it often affects the flowability of a granulate. In this paper the definition of fines is arbitrarily set as particles smaller than 100 μm. Fig. 3 gives the degree of fines formation as a result of milling of the different formulations. The crack propagation theory by Subero and Ghadiri (2001) leads to the prediction that the formulation containing lactose 100 M would suffer from the most intense fines formation. Interestingly, this is not

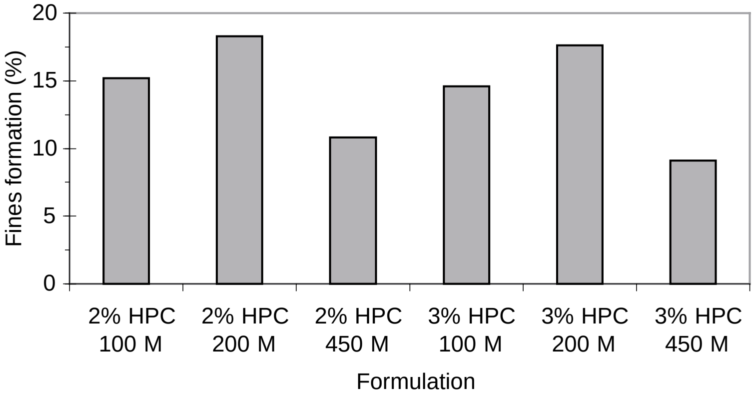

Fig. 3. Formation of fine particles (<100 μm) from the different formulations (milling conditions as in Fig. 1).

the case, as the lactose monohydrate 200 M formulation shows the largest fines formation.

The reason for the small amounts of fines formed of lactose monohydrate 100 M is that during milling the granules will break, while the primary particles will remain largely intact. Because lactose monohydrate 100 M is practically free from particles smaller than 100 μm, only limited fines will be formed. Most likely, the fines formed during milling of the lactose 100 M formulation will be rich in corn starch because these particles are smaller than the lactose particles (Table 2). The effect of HPC on fines formation is limited although more HPC is suggested to lead to less fines formation (Fig. 3). This is consistent with the results of Airaksinen et al. (2000) where granules with higher binder contents show less friability.

3.2. *Influence of mill settings on breakage properties of one formulation*

The purpose of this part of the study is to evaluate the effects of alterations in mill settings on size reduction of one typical granulate. The composition of the model granules consist of 87% lactose 200 M, 10% corn starch and 3% HPC. There will, however, always be an effect of the granule size distribution of the material that feeds the mill. This is illustrated by Fig. 4, which shows linear relationships between the

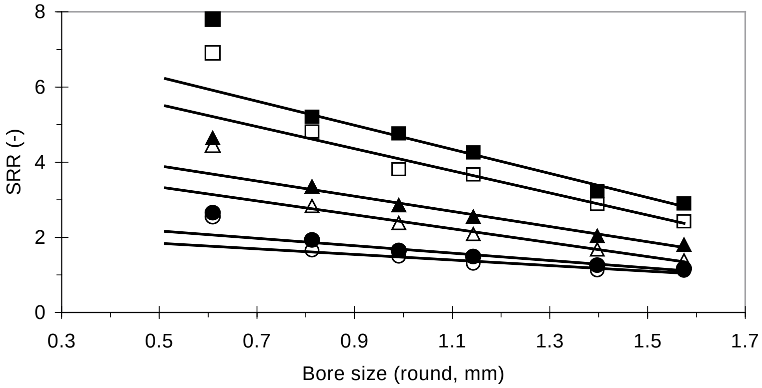

Fig. 4. Size reduction ratio as a function of mesh width of screen (all screens with spherical bores). Legend: (○, ●) granule size fraction: 1.00–1.60 mm; (△, ▲) granule size fraction: 1.60–2.00 mm; (□, ■) granule size fraction: 2.00–3.15 mm. Open symbols impeller rate 750 rpm, closed symbols impeller rate 1500 rpm (formulation lactose 200 M and 3% HPC).

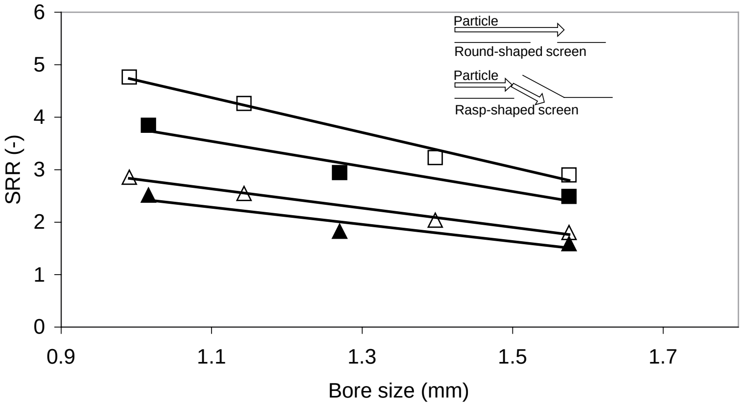

Fig. 5. Relation between screen type and size reduction ratio at an impeller rate of 1500 rpm. Legend: (△, ▲) granule size fraction: 1.60–2.00 mm; (□, ■) granule size fraction: 2.00–3.15 mm. Open symbols: round screens, closed symbols: rasp screens (formulation lactose 200 M and 3% HPC). The inserted picture gives schematic drawings of the round (upper drawing) and rasp screen (lower drawing) and the particle trajectories.

size reduction ratio and the bore sizes of the sieves in the Comil (as long as the bores are equal to or larger than about 0.8 mm).

Evidently, an increase in mesh widths of the sieves results in less size reduction. The influence of the sieve bores become larger when the feed material becomes coarser, as is expressed by the increasing slopes of the lines for the coarser materials in Fig. 4. Alterations in impeller rate appear to have a similar effect on the size reduction, although it is noted that the impeller rate effect is much smaller than the other effects. Changes in impeller rate are more important when the feed material is coarse. The data so far indicate that mill settings become more critical, and the milling process less controllable when the material to be milled becomes coarser. This is also visible when very small sieve bores are used (0.61 mm), where the degree is size reduction is apparently higher than expected from linear extrapolation of the other results. Most likely, this is due to increased residence times in the mill. Small bores make it difficult for a granulate to leave the screen. This results in more impacts to granules which already reached the size that enables transport through the screen. This implies a wider distribution and finer particles (e.g. Klimpel, 1996). Therefore, screens with bores of less than 0.8 mm are not desired for the type of granules tested here.

The discussion so far shows that the possibilities of a milled granulate to leave the screen determines the particle size distribution of the milled material. This implies that screen type has an effect on the degree of size reduction. Fig. 5 compares the effect of the two screen types (spherical bores versus rasped bores, see inset in Fig. 5). The figure shows that there is a measurable effect of screen type on the degree of size reduction: a sieve with round bores results in more size reduction than the one with the rasp-shaped bores. The type of the screen affects the residence time of the granulate in the mill and therefore the size reduction. The rasp sieve will force the in-size granules to leave to the mill (inset in Fig. 5). Again, the effects of multiple impacts are visible. It is more difficult for in-size granules to leave the screen when bores are spherical. This leads to impacts on these small or in-size particles and hence a finer milled product. The type of screen has more influence when the starting material is coarser.

Mill settings have a major influence on the granule size after milling, however, not all parameters influence the size reduction at an equal level. The most important parameter is the size of the bores in the screen. It is clear that a reduction in bore size leads to more size reduction due to multiple impacts. A coarser granulate results in finer particles after milling when the same mill settings are used. This conclusion leads to a paradox: for a coarser milled product, the mill must be fed with a finer granulate.

For a granulate that can easily be used in further unit operations, it is important that the granulate contains a limited amount of fine material. This is because

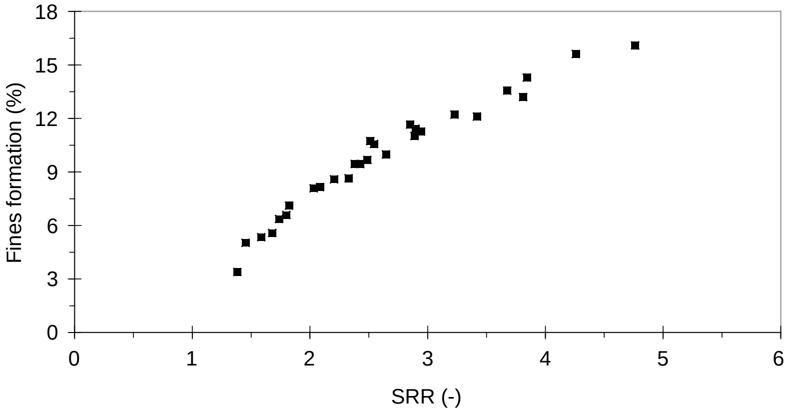

Fig. 6. Influence of the size reduction ratio on the formation of fines (formulation lactose 200 M and 3% HPC).

practical experience reveals the fine particles often lead to segregation and sometimes to out of specifications products. For this reason fines formation during milling must be limited as much as possible or at least be controlled. During milling experiments an amount of very fine particles is produced. When, for all the experiments (with the same granule formulation, but all mill settings), the formation of fines is plotted as a function of the size reduction ratio (Fig. 6) a unique and almost linear relation has been found.

From Fig. 6 it appears that it is the degree of size reduction that determines the amount of fines formed. It seems that none of the parameters varied (i.e. screen size, screen type, impeller speed, particle size feed material) has an influence on the formation of fines only. When the formation of fine particles has to be limited, milling in multiple steps with decreasing screen bores is an option. Moreover, a sieving step to separate the fines from the granulate is necessary. Another option is, if possible, to feed a mill with a finer material in order to reduce the dust formation. This conclusion has frequently been drawn (e.g. Klimpel, 1996), and it appears that these granulates are no exception to this rule.

4. Conclusions

From this study it appears that both the formulation and the mill settings play important roles in the size reduction of granules. With respect to formulation, the granule strength plays the dominant role in the breakage behavior of the particles. The strength of the granules is mainly determined by initial particle size of the building blocks of the granule. The amount of binder used also plays a role here, but it is less important. A finer initial particle size of the building blocks of the granules leads to less size reduction and formation of fines due to crack branching at the binding sites of the particles.

Regarding the mill settings, it is possible to mill agglomerates to a defined particle size. However, it is not possible to influence the formation of fines only because this is always related to the total degree of size reduction. When a high size reduction is required and the formation of fines has to be limited, a multiple step milling procedure with separation of in-size particles is necessary. Additionally, feeding a mill with a finer material will automatically lead to less fines formation.

Acknowledgements

The oral dosage form development groups at Organon’s Department of Pharmaceutics and Wim Pries from the Powder Technology Group of Akzo Nobel Polymer Chemicals Laboratory Deventer are kindly acknowledged for their experimental support and fruitful discussions.

References

Airaksinen, S., Antikainen, O., Rantanen, J., Yliruusi, J., 2000. Advanced testing of granule friability determined from size reduction data. Drugs Made in Germany 43, 96–99.

Klimpel, R.R., 1996. International Natural Fine Particle Research Institute Review Report SAR 12-14.

Mishra, B.K., Thornton, C., 2001. Impact breakage of particle agglomerates. Int. J. Miner. Process. 61, 225–239.

Narayanan, S., 1986. Single particle breakage tests: a review of principles and applications to commination modelling. Bull. Proc. AIMM, 49–58.

Pietsch, W., 1991. Size Enlargement by Agglomeration. John Wiley & Sons Ltd., Chichester, UK, pp. 30–33.

Rumpf, H., 1970. Zur Theorie der Zugfestigkeit von Agglomeraten bei Kraftübertragung an kontaktpunkten. Chem. Ing. Techn. 42, 538–540.

Subero, J., Ghadiri, M., 2001. Breakage patterns of agglomerates. Powder Technol. 120, 232–243.

Vogel, L., Peukert, W., 2002. Characterisation of grinding relevant particle properties by inverting a population balance model. Part. Part. Syst. Charact. 19, 149–157.