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Granule fraction inhomogeneity of calcium carbonate/sorbitol in roller compacted granules

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Abstract

The granule fraction inhomogeneity of roller compacted granules was examined on mixtures of three different morphologic forms of calcium carbonate and three particle sizes of sorbitol. The granule fraction inhomogeneity was determined by the distribution of the calcium carbonate in each of the 10 size fractions between 0 and 2000 μm and by calculating the demixing potential. Significant inhomogeneous occurrence of calcium carbonate in the size fractions was demonstrated, depending mostly on the particles sizes of sorbitol but also on the morphological forms of calcium carbonate. The heterogeneous distribution of calcium carbonate was related to the decrease in compactibility of roller compacted granules in comparison to the ungranulated materials. This phenomenon was explained by a mechanism where fracturing of the ribbon during granulation occurred at the weakest interparticulate bonds (the calcium carbonate: calcium carbonate bonds) and consequently exposed the weakest areas of bond formation on the surface of the granules. Accordingly, the non-uniform allocation of the interparticulate attractive forces in a tablet would cause a lowering of the compactibility. Furthermore, the ability of the powder to agglomerate in the roller compactor was demonstrated to be related to the ability of the powder to be compacted into a tablet, thus the most compactable calcium carbonate and the smallest sized sorbitol improved the homogeneity by decreasing the demixing potential.

Keywords: Granule inhomogeneity; Roller compaction; Dry granulation; Compactibility; Morphology; Particle size

1. Introduction

Granulation of pharmaceutical powder blends is generally expected to generate a fixed state of mixing and consequently prevent demixing of the drug from the excipients. However, a heterogeneous drug distribution in different granule size fraction has been observed (Lachman and Sylwesterowicz, 1964; Cox et al., 1968; Ojile et al., 1982). Similarly, a non-uniform distribution of binder in granule size fractions was reported for wet processed granules (Knight et al., 1998; Scott et al., 2000; Johansen and Schaefer, 2001). Agglomerated materials normally have a particle size distribution that may potentially segregate when pouring and handling. During tabletting of granulated material in a tablet press, coarser granules in the hopper will have a tendency to role over the powder surface and separate from the fine material. Consequently, if the drug is distributed non-uniformly in the granule fractions, tablets compressed at different stages in the tabletting process will contain varying amounts of drug, causing critical high levels in the tablet content uniformity.

The inhomogeneity of the drug distribution as a function of the granule size fractions has been successfully expressed as the demixing potential (DP%). The DP% specify the coefficient of variation of a component in the different size fractions of carrier material as a quantification of the latent ability to segregate (Thiel and Nguyen, 1982). It follows that the demixing potential does not necessarily predict whether the segregation actually will occur, because aspects as powder flow properties and mechanical manipulation are affecting the risk of segregation.

In roller compacted granules, a non-uniform distribution of excipients was reported in granule fractions as a smaller proportion of microcrystalline cellulose (MCC) was found in the fines

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than in the coarse granules (Grulke et al., 2004a,b). The granule fraction inhomogeneity was explained by the authors as a mechanism where the plastic deforming MCC surrounded the brittle materials and absorbed most of the energy which resulted in a lesser degree of fragmentation of the brittle materials. Consequently the brittle materials were insufficiently compressed and were unable to cohere.

In the literature concerning wet granulation, the particle size of primary particles has been demonstrated to impact the drug and binder distributions. Vromans et al. (1999) reported that smaller sized excipient increased the mechanical strength of the granule nuclei during wet massing, which was related to an improvement of the drug distribution. Moreover, micronizing the drug and excipient were shown to minimize the heterogeneity of the drug distribution in granule size fractions (Egermann and Reiss, 1988). Wet granulation of powder mixtures resulted in accumulation of the finest particles in the larger granules which was explained by a process where the finer particles penetrates the pores in the granules (Van den Dries and Vromans, 2003).

In our previous study of roller compacted granules, the morphology of calcium carbonate and the particle size of sorbitol were shown to have significant impact on the compaction properties (Bacher et al., 2007). The different compaction properties of the starting materials were expected to affect the granule fraction inhomogeneity as well.

Therefore in this study, the aim was to investigate the granule fraction inhomogeneity of granules manufactured by roller compaction from mixtures of three different morphologic forms of calcium carbonate and three particle sizes of sorbitol. The granule fraction inhomogenity was evaluated by determining the distribution of the calcium carbonate in the 10 size fractions and by calculating the demixing potential.

2. Materials and methods

2.1. Materials

Calcium carbonate (Mikhart 65 (Provencale S.A., France), Scoralite (SCORA, France) and Sturcal L (Specialty Minerals Lifford, PA)).

Sorbitol (C*Sorbidex P166B0 (Cerestar, Belgium), C*Sorbidex P16656 (Cerestar, Belgium) and Neosorb P100T (Roquette, France)).

Magnesium stearate (Peter Greven C.V., The Netherlands) were used as starting materials.

The label codes Mikhart for Mikhart 65, Scoralite for Scoralite, Sturcal for Sturcal L, Sorbitol-45 for C*Sorbidex P166B0, Sorbitol-130 for Neosorb P100T and Sorbitol–236 for C*Sorbidex P16656 are applied. The sorbitol indexes refer to the mean particle size. Morphology and particles size (measured by laser diffraction) are given in Bacher et al. (2007).

2.2. Methods

2.2.1. Preparing the powders for direct compression

The blends were prepared as described in Bacher et al. (2007).

Table 1
The demixing potential (DP%) of calcium carbonate/sorbitol granules

	Mikhart	Scoralite	Sturcal
Sorbitol-45	2.4	4.6	1.7
Sorbitol-130	12.1	19.9	6.6
Sorbitol-236	30.9	31.3	13.8

2.2.2. Roller compaction

The roller compacted granules were manufactured as described in Bacher et al. (2007) with the setting of experiment 2 in Table 1.

2.2.3. Compression on a compaction simulator

The granules were compressed on a compaction simulator as described in Bacher et al. (2007).

2.2.4. Characterization of powders, granules and tablets

Sieving analysis is performed as described in Bacher et al. (2007).

The demixing potential quantifies the variation in the component content in powder and granule size fractions. The demixing potential (DP%) is calculated as (Thiel and Nguyen, 1982):

$$\mathrm{DP\%} = \frac{100}{\bar{p}}\sqrt{\sum \frac{w}{100}(p-\bar{p})^2} \quad (1)$$

In which p is the proportion of the specific component in a particular size fraction and w is the weight of the particular fraction. The mean composition ($\bar{p}$) is calculated as the mean content of the mixture:

$$\bar{p} = \frac{\sum pw}{\sum w} \quad (2)$$

The proportional component (p) was calculated as the percentage calcium carbonate in each of the granule fractions from the sieving analysis. The quantity of calcium carbonate was estimated by titrating accordingly the monograph (USP NF, 2004) $N=2$.

The proportional component (p) and the weight (w) for the mixtures of the ungranulated starting materials were estimated from the particle size distributions of the starting materials, divided into the same fractions as the granules. The particle size distributions were determined by a laser diffraction particle sizer (Malvern Mastersizer S 2601Lc, Malvern, UK) fitted with a dry powder feeder and operated at 3 bars.

The compactibility C_P was determined as described in Bacher et al. (2007).

2.2.5. Experimental set-up

Nine binary blends of three calcium carbonate and three sorbitol grades, in a 76:24 ratio were dry granulated in a roller compactor. The granule fraction inhomogeneity was evaluated and compared with the compactibility of the ungranulated starting materials.

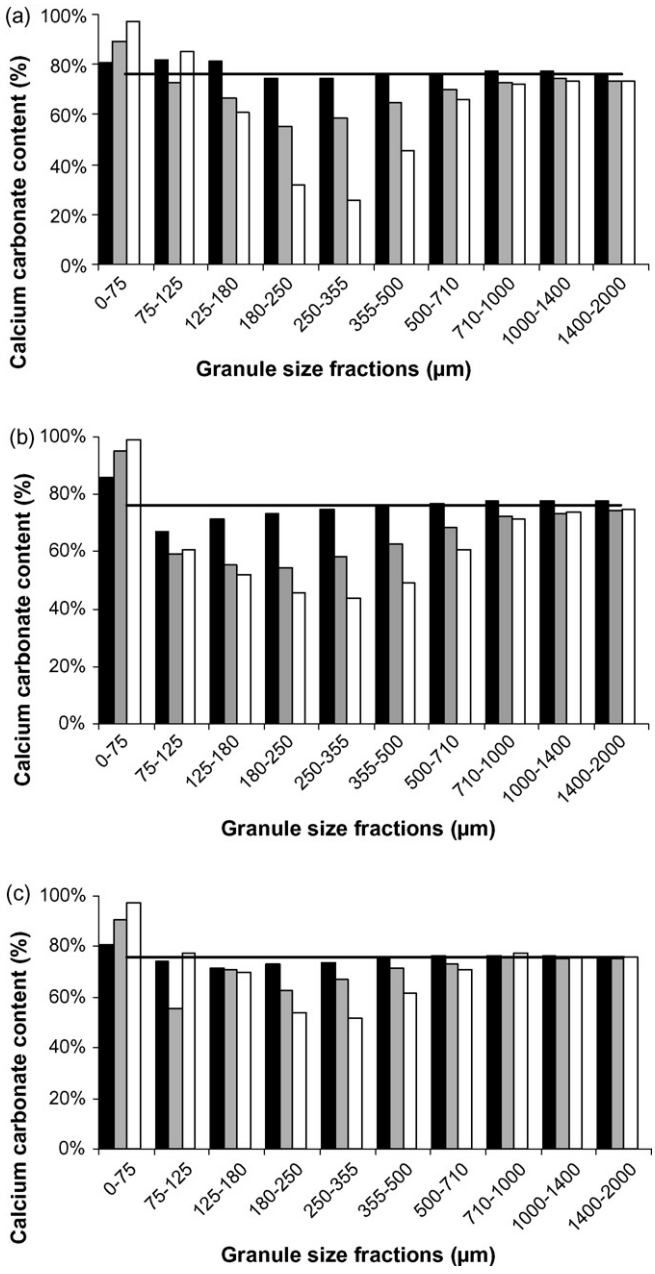

Fig. 1. The relative calcium carbonate content in the granule fractions. The line represents the theoretically quantity of 76%. (a) Black columns are Mikhart/sorbitol-45, gray columns are Mikhart/sorbitol-130 and the white columns are Mikhart/sorbitol-236. (b) The Black columns are Scoralite/sorbitol-45, gray columns are Scoralite/sorbitol-130 and the white columns are Scoralite/sorbitol-236. (c) Black columns are Sturcal/sorbitol-45, gray columns are Sturcal/sorbitol-130 and the white columns are Sturcal/sorbitol-236.

3. Results and discussion

3.1. Calcium carbonate distribution in granule fractions

The calcium carbonate distributions in the granule size fractions are presented in Fig. 1. Generally, the Scoralite content in the granule fractions showed the most inhomogeneous pattern followed by Mikhart; whereas the Sturcal granule fractions were more evenly distributed. This is possibly caused by the ability of the calcium carbonate to form bonds. The milled irregular particles of Mikhart form more easily bonds than the fairly smooth Scoralite; due to the larger surface area and perhaps also due to the higher electrostatic charges on the edges of Mikhart (Bacher et al., 2007). Sturcal form the strongest bonds as the surface area is larger and it is likely to form bonds by mechanical interlocking (Bacher et al., 2007).

The particle size of sorbitol affected the calcium carbonate distributions in the granule fractions as decreasing sorbitol particle size increased the homogeneity. The calcium carbonate content in the granule fractions of the small sized sorbitol were close to the average content, while sorbitol-130 and sorbitol-236 had a prevalence of calcium carbonate in the fines <75 μm and in the coarse granules >710 μm (Fig. 1a–c). This can be related to the increasing bonding ability of decreasing particle sizes of sorbitol due to the enlargement of the surface area (Bacher et al., 2007). A slightly increased calcium carbonate proportion was expected to be found in fractions below 125 μm, since only 50 and 25% of sorbitol-130 and sorbitol-236, respectively were able to pass the 125 μm sieve. This assumption is provided that the particles stay intact during roller compaction. The maximum sorbitol level (estimated as the minimum calcium carbonate level) were detected in decreasing fractions with decreasing particle sizes of sorbitol; thus sorbitol-236 were most dominant in fraction 250–355 μm and sorbitol-130 were most prevalent in fraction 180–250 μm. Overall, the highest occurrence of sorbitol-45 could be found in fraction 125–180 μm. This is probably also related to the particle size distribution of the sorbitols and the small proportion of sorbitol in the composition, which decreases the possibility of more than a few sorbitols particles in the same granule.

Since heterogeneity has been demonstrated, the granule size distribution was also investigated. Some representative granule size distributions are exemplified in Fig. 2.The three morpho-

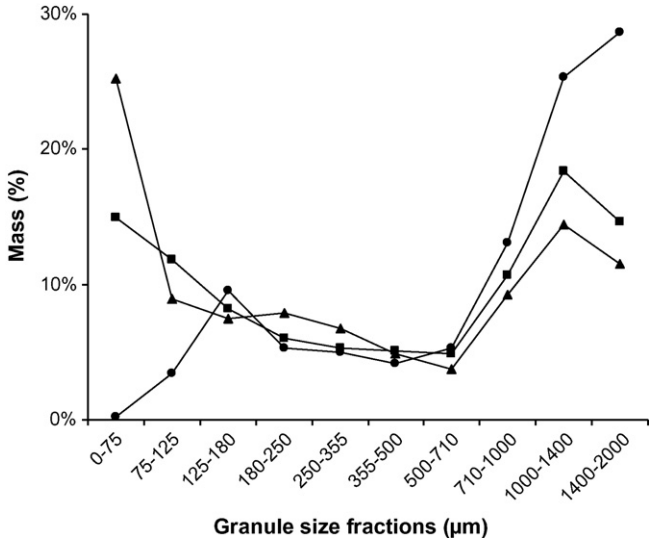

Fig. 2. Examples of the granule size distributions of different calcium carbonates with sorbitol-130: (■) Mikhart/sorbitol-130, (▲) Scoralite/sorbitol-130 and (●): Sturcal/sorbitol-130.

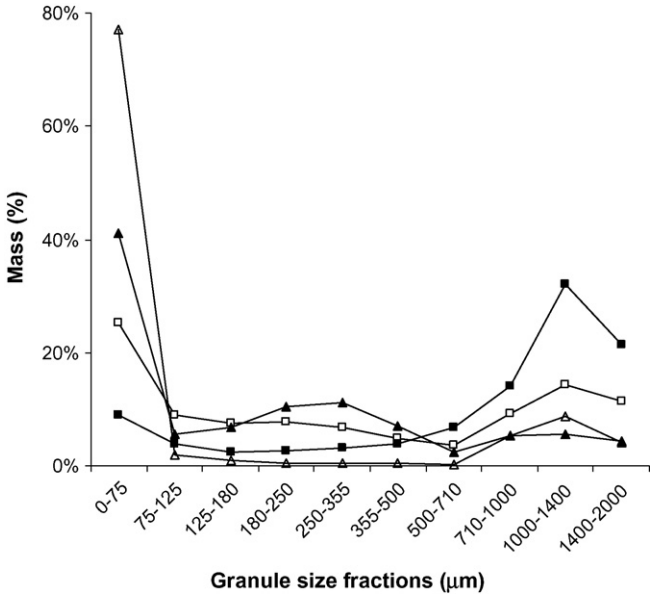

Fig. 3. An example of the granule size distribution of calcium carbonate with and without sorbitol: (■) Scoralite/sorbitol-45, (□) Scoralite/sorbitol-130, (▲) Scoralite/sorbitol-236 and (△) Scoralite.

logical forms of calcium carbonate generated different granule size distributions in the granules of calcium carbonate and sorbitol. Sturcal had a low-absolute quantity of the fines < 75 μm, resulting in a larger homogeneity. The proportion of non-agglomerated material of Scoralite and Mikhart granules with sorbitol-236 was twice as large as for the sorbitol-130 granules and four times as large as for the sorbitol-45 granules. From the representative particle size distributions in Fig. 3, it is noticed that the fractions between 125 and 710 μm were enlarged by the sorbitol which resulted in a decrease in fines in comparison to the granules without sorbitol.

The calcium carbonate distribution in the granule fractions is a product of the ability of the powders to form interparticulate bonds during roller compaction and the grinding of the ribbons. The stronger interparticulate attractive forces of sorbitol were evident as the sorbitol mainly existed as agglomerates. Moreover, the sorbitol was likely to be situated primarily inside the granules surrounded by calcium carbonate at the surface. This can be explained as the fracturing of the ribbon mainly occurred at the weakest interparticulate bonds (the calcium carbonate: calcium carbonate bonds) and thus only the strongest bonds resisted the force of the granulator. For this reason, the compression of roller compacted granules into tablets is affected as the intergranulate bonds appears to be generated between the weakest areas of bond formation. The non-uniform allocation of the interparticulate attractive forces in a tablet might explain the decrease in tablet compactibility of roller compacted granules compared to powders since a fracture in a tablet can be initiated more easily. The decrease in tablet compactibility of roller compacted granules in comparison to the starting materials has been reported widely (Inghelbrecht and Remon, 1998; Freitag and Kleinebudde, 2003; Bacher et al., 2007).

Table 2
The theoretical demixing potential (DP%) of calcium carbonate/sorbitol powder blends

	Mikhart	Scoralite	Sturcal
Sorbitol-45	6.6	26.5	26.5
Sorbitol-130	21.5	43.7	43.7
Sorbitol-236	38.7	49.7	49.7

3.2. Demixing potential

The demixing potential quantifies the distribution of calcium carbonate as a weighted function of the granule size. The demixing potential is a measure of variation and can be directly compared with the relative standard deviation. If all the fractions contained the same amount of calcium carbonate, the demixing potential would be 0. The demixing potential for the roller compacted granules is depicted in Table 1 where a smaller sized sorbitol showed a low demixing potential. The Sturcal granules also had a lower demixing potential than the Mikhart and Scoralite granules. The demixing potential of the granules are lower than the theoretical value of the corresponding starting materials (Table 2). This indicated that roller compaction of calcium carbonate and sorbitol improved the fixation of the mixing state to some extend. However the possibility of the powder blends and the granules to demix are expected to be minimal due to the limited flow properties (Bacher et al., 2007). Additionally, during static conditions the edgy shaped granules are likely to lock the positions of the granules, making the demixing even more improbable.

The morphology of the calcium carbonate and the size of sorbitol which were related to a high compactibility in

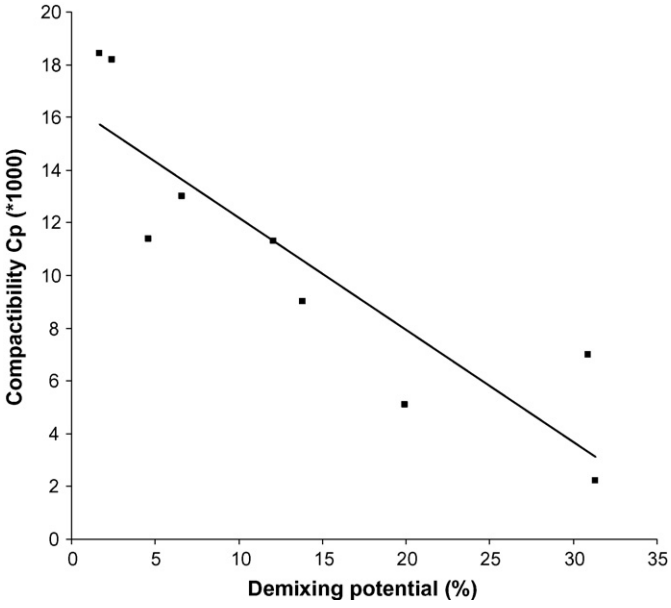

Fig. 4. Correlation between the demixing potential and the compactibility C_P of the powder blends. The relative standard deviation of the slope is 19.3%.

direct compression (Bacher et al., 2007), also improved the agglomeration formation and the uniformity of calcium carbonate in granule fractions. Therefore a relationship between the compactibility C_P and the demixing potential of the direct compressible tablets were depicted (Fig. 4). The more compactable the powder blends were, the smaller became the demixing potential. The correlation seems reasonable since the same phenomenon is most likely to occur in both the cases of the fracturing of at tablet in a diametral compression tester as well as the fracturing of the ribbon in a granulator.

The relationship between the demixing potential of roller compacted granules and the compactibility C_P of direct compression supports the relevance of applying the low-pressure compression of tablets (slugging) as a simulation of the roller compaction. The simulation of the roller compactor has the published by Zinchuk et al. (2004).

4. Conclusion

Inhomogeneous calcium carbonate distributions were demonstrated and the distributions were affected mostly by the particle size of sorbitol and to a minor degree by the morphological forms of calcium carbonate and, thus yielding different demixing potentials. The ribbons are expected to fracture at the weakest interparticulate bonds (the calcium carbonate: calcium carbonate bonds) during granulation, which causes a non-uniform distribution of the weakest area of bond formation in tablets of dry granules and explains the decrease in compactibility.

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