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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.