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Compressibility and compactibility of granules produced by wet and dry granulation

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ABSTRACT

The bulk properties, compactibility and compressibility of granules produced by wet and dry granulation were compared applying a rotary tablet press, three different morphological forms of calcium carbonate and two particle sizes of sorbitol. Granules from both granulation methods possessed acceptable flow properties; however, the ground (Mikhart) and cubic (Scoralite) calcium carbonate demonstrated better die-filling abilities in the tablet press than the scalenhedral calcium carbonate (Sturcal). The wet processed granules showed in general larger compression properties. This was explained as these granules were mechanical stronger and had a higher initial porosity. In some cases, a large particle surface area of calcium carbonate and sorbitol resulted in a small, insignificant improvement of the consolidation characteristics. A correlation between the compression and compaction characteristics was demonstrated.

1. Introduction

In the field of pharmaceutical powder compaction, it is often necessary to improve the material flow properties in order to obtain a uniform die-filling in a tablet press. The flow properties can be enhanced by converting fine powders into larger agglomerates. Wet granulation is traditionally applied because the equipment and knowledge are available. In wet granulation, a fluid binder is distributed on a powder blend and subsequently the granules are dried. A more cost efficient alternative is the dry process—roller compaction where the material is densified between two counter rotating rolls under pressure forming a compact ribbon, which is milled into granules. This fairly simple technique is especially applicable for voluminous materials as it enhances the bulk density greatly. The disadvantages of the roller compaction comprise the formation of a relative large amount of dust and fines (Inghelbrecht and Remon, 1998) and the decrease in the compaction properties of powders (Bacher et al., 2007a; Sheskey and Hendren, 1999; Freitag et al., 2004).

Differences in compression of wet and dry granulated material are observed as wet processed granules often are more voluminous and roller compacted granules more dense than the original powder mixture (Sheskey and Hendren, 1999). Large granule porosity in wet processed granules has been related to a large fragmentation during compaction, resulting in mechanical stronger tablets (Wikberg and Alderborn, 1991). Similar results were obtain by Zuurman et al. (1994) who reported a positive relationship between the mechanical strength and the total porosity in the granule powder bed before compaction.

The geometric shape of the granules influences the volume occupied by intergranular voids in the powder bed before compaction; thus the granule morphology may affect the compression properties. Tablets made of rounded pellets, having the same intra-agglomerar porosity as irregular granules had a lower tensile strength due to a smaller interagglomerar void of the rounded pellets (Johansson and Alderborn, 2001). Agglomerates of different morphology are generated from wet and dry processing, thus Sheskey and Hendren (1999) characterised granules made in a high shear mixer as being rounded and course surfaced while granules from a roller compactor appeared smooth surfaced. In addition, Bacher et al. (2007a) described the roller compacted granules as edgy shaped.

The morphology of primary particles in granules has been demonstrated to affect the compressibility and the compactibility (Bacher et al., 2007a; Freitag et al., 2004). Generally, it is assumed that a decreased primary particle size increases the tablet strength

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(Alderborn, 1996). However, this assumption is provided that the particles stay intact during compaction.

In this study, the aim was to investigate and characterize granules from a wet and a dry process and compare the compressibility and compactibility. The granules were composed of three different morphologic forms of calcium carbonate and two particle sizes of sorbitol.

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) and Neosorb P100T (Roquette, France)).

Povidone (Povidone 30, BASF, Germany).

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 and Sorbitol-130 for Neosorb P100T are applied. The indexes of sorbitol refer to the mean particle size. Details about morphology and particles size are published in Bacher et al. (2007a).

2.2. Methods

2.2.1. Roller compaction

Calcium carbonate and sorbitol were sieved through an oscillating sieve (Frewitt Granulator MGI 312, Frewitt, Switzerland) with a sieve screen size of 600 μm. Calcium carbonate and sorbitol, in a 76:24 ratio, were mixed in a planetary blender (Bear Varimixer R 60, Bear Varimixer, Denmark) equipped with a 60 l container and a large mixing aggregate. A total of 80 kg of each blend were mixed for 10 min at 53 rpm. For blends containing Scoralite or Mikhart the partial batch size was 40 kg while the lower bulk density of Sturcal required three partial batches of 26.7 kg.

Granules were prepared on an instrumented production scale roller compactor (GMP-Polygran Rollerpress 250/100/3, Gerteis, Switzerland). The hopper was equipped with a 10-blade lump breaker. The feed and tamp augers were operated at a speed of 4.2 and 5.9 rpm respectively, thus the tamp/feed ratio was set to 140%. Since the gap size depends on the amount of delivered materials in the nip zone, it was automatic adjusted between 0.9 and 2.2 mm depending on the bulk properties of the materials and the speed of the augers. The roller compactor was fitted with knurled rolls, operated at a compaction force of 12 kN/cm and a roller speed at 3 rpm. The ribbons were ground into granules in the oscillating pocket mould grooved rotor set at a speed of 80 rpm in each directions and a rotor angle of 360°/390°. The granulator screen was 2.0 mm.

2.2.2. Wet granulation

5 kg calcium carbonate and sorbitol were sieved manually (300 μm) and dry mixed in a 25 l high shear mixer (Fielder PMA 25, T.K. Fielder, Denmark) in the mass ratio 76:24 for 1 min at an impeller speed of 120 rpm. The granulating fluid was produced by adding 100 g povidone slowly into stirring hot water (70–80 °C) and cooled down to room temperature before use. Keeping the binder content constant, the amount of water in the granulating fluid was varied according to the variation in the surface areas: Hence the povidone concentration was 34% for Mikhart/Sorbitol-45 and Scoralite/Sorbitol-45, 32% for Mikhart/Sorbitol-130 and Scoralite/Sorbitol-130, 20% for Sturcal/Sorbitol-45 and 19% for Sturcal/Sorbitol-130. The granulating fluid was atomized through a nozzle with an opening of 1 mm over 2 min while the impeller speed was set to 280 rpm and the chopper was activated. Wet massing was continued for 3 min at the same settings. The wet granules were transferred to a fluid bed dryer (Aeromatic MP 1, Aeromatic-Fielder AG, Switzerland) where the granules were dried at an inlet air temperature of 50 °C to a product temperature of 40 °C. The air volume was adjusted to reach a differential pressure over the perforated bottom from 2000 Pa at start to 300 Pa in the end of the drying. Loss on drying was performed at 80 °C (HR73 Halogen moisture analyzer, Mettler Toledo, Switzerland) in order to assure that the water content was below 0.5% w/w.

2.2.3. Compaction

The granules were mixed with 0.34% magnesium stearate for 5 min at 25 rpm in an 8 l cubic blender (Erweka AR400, Erweka, Germany) with an affixation angle of 45°.

The lubricated granules were compacted on an instrumented 6-station rotary tablet press (Korsch PH106, Korsch AG, Germany). The tablet press was operated with 3 round, flat faced and edged punches with a diameter of 14 mm at 8.000 tablets per hour. Tablets with a mass of 1.75 g were produced at five compaction forces in the compaction range: 1–25 kN.

The tablet mass variation was determined by measuring the weight of 10 randomly drawn tablets at each compression force (in total 50 tablets) using an automated in process control equipment (Schleuniger tablettester 8 M, Dr. Schleuniger Pharmatron, Switzerland).

Additionally, tablets were manufactured on a compaction simulator as described in Bacher et al. (2007a).

2.2.4. Characterization of granules and tablets

Scanning electron micrographs (JSM-5200 Scanning Microscope, Jeol, Japan.) were prepared using samples spotted with gold (Bio-Rad Polaron Division E 5200 Auto Sputter, Bio-Rad, UK). Samples consisted of granules from the size fraction: 180–1000 μm.

The bulk density was evaluated by applying the test for apparent volume (European Pharmacopoeia, 2.9.15, 2005).

The intragranular porosity of the agglomerates was estimated by a mercury immersion method as described by Strickland et al. (1956). A sample of 3–4 g granules from the size fraction: 180–1000 μm was placed in a glass pycnometer and degassed to a pressure of 80 mmHg. The pycnometer was filled with mercury and the apparent volume of the sample was estimated by mercury displacement at an intrusion pressure of 740 mmHg. At this intrusion pressure, mercury will penetrate into pores with a diameter greater than 20 μm (Johansen and Schæfer, 2001). Duplicate measurements of the apparent volume were performed. The intragranular porosity was determined on basis of the apparent volume and the volume of the ground material from the same size fraction. The granules were ground in a coffee mill (Braun 4041, Braun AG, Germany) for 1 min. The volume of the ground material was determined in a helium pycnometer (Accupyc 1330, Micromeritics instrument corporation, USA).

The compressibility index (CI) (Carr, 1965) was estimated from the bulk and tap volumes (V_{bulk} and V_{tap}) measured according to the test for apparent volume (European Pharmacopoeia, 2.9.19, 2005):

$$CI\% = \frac{V_{bulk} - V_{tap}}{V_{bulk}} \cdot 100\% \quad (1)$$

The specific crushing strength (SCS) of the tablets is determined for a cylindrical tablet where the crushing force (F) is normalized by the cross-sectional area (diameter (d)·height (h)).

$$SCS = \frac{F}{d \cdot h} \quad (2)$$