International Journal of Pharmaceutics 414 (2011) 131–139

Contents lists available at ScienceDirect

International Journal of Pharmaceutics

journal homepage: www.elsevier.com/locate/ijpharm

A compressibility and compactibility study of real tableting mixtures: The impact of wet and dry granulation versus a direct tableting mixture

Maja Šantl[a], Ilija Ilić[b], Franc Vrečer[a,b], Saša Baumgartner[b,*]

[a] Krka d.d., Novo Mesto, Šmarješka cesta 6, 8501 Novo Mesto, Slovenia
[b] Faculty of Pharmacy, Aškerčeva 7, 1000 Ljubljana, Slovenia

ARTICLE INFO

Article history:
Received 21 January 2011
Received in revised form 3 May 2011
Accepted 5 May 2011
Available online 12 May 2011

Keywords:
Wet granulation
Dry granulation
Compressibility
Compactibility
Heckel
Waker

ABSTRACT

The purpose of this study was to investigate the influence of various powder agglomeration processes on tableting mixture flow and compaction properties. Four different granulation methods of the same model placebo formulation were tested at a semi-industrial scale and their properties were compared to those of the directly compressed mixture. The wet granulated mixtures had superior flow properties compared to other mixtures and showed better compressibility, measured by the Heckel and Walker models. This was attributed to work hardening due to the double particle processing and also to shorter contact times due to higher initial densities of dry granulated mixtures, allowing a shorter time for deformation. A strong linear correlation was established between the Heckel and Walker coefficients, which was further confirmed by the net energy results of force–displacement measurements. It was shown that the Walker model had slightly better discriminative power to differentiate tableting mixtures according to compressibility. The compactibility was considerably lower for the slugged mixture; however, the roller-compacted mixture produced tablets with unexpectedly high tensile strength. In conclusion, it is important to emphasize that general assumptions like higher porosity ⇒ better compressibility or better compressibility ⇒ better compactibility cannot be established for complex tableting mixtures.

1. Introduction

Successful compaction and tableting of pharmaceutical powders requires a profound understanding of the fundamental properties of powders. These include physicochemical and mechanical properties, both of which dictate how formulations behave during tablet processing.

In the pharmaceutical industry, the preferred tablet production method is direct tableting. However, it is often necessary to improve the material's compaction and flow properties in order to obtain uniform die-filling and to produce tablets of adequate quality. These properties are commonly enhanced by converting fine powders into larger agglomerates by the process of wet or dry granulation. Wet granulation is traditionally used; this process consists of distributing the liquid binder in a powder blend followed by drying the agglomerates produced. This can be achieved using high-shear or fluid-bed technology. Alternatively, dry granulation (i.e., slugging or roller compaction) can be used to produce agglomerates. Dry granulation consists of a compaction step followed by a milling step. During slugging, the primary compaction step is performed using a conventional tablet press, whereas during roller compaction the powder mixture is passed between two rotating cylindrical rollers to form a compact ribbon that is further broken down into a product of granular size and then recompressed (Armstrong, 2007). Dry granulation has some advantages and disadvantages compared to wet granulation. It is a fairly simple technique, which should be more cost effective and can greatly improve the bulk density of voluminous materials. Dry granulation does not require water or organic solvents, thus making it an attractive method for moisture- and heat-sensitive drugs (Kleinebudde, 2004). However, it produces a relatively large amount of dust and fines (Herting and Kleinebudde, 2007; Inghelbrecht and Remon, 1998; Kleinebudde, 2004) and impairs the compaction properties of powders (Bacher et al., 2007; Freitag et al., 2004; Herting and Kleinebudde, 2007).

The compaction properties of pharmaceutical powders are characterized by their compressibility and compactibility. Compressibility is the powder's ability to deform under pressure, and compactibility is the ability to form mechanically strong compacts (Leuenberger, 1982; Sonnergaard, 2006). Three stages of this process can be distinguished during powder compaction: (i) rearrangement and powder densification due to increasing pressure; (ii) fragmentation of agglomerates; and (iii) fragmentation and deformation (both reversible elastic and irreversible plastic) of pri-

* Corresponding author at: Department of Pharmaceutical Technology, Faculty of Pharmacy, University of Ljubljana, Aškerčeva 7, SI-1000 Ljubljana, Slovenia.
Tel.: +386 1 47 69 633; fax: +386 1 42 58 031.
E-mail address: sasa.baumgartner@ffa.uni-lj.si (S. Baumgartner).

0378-5173/$ – see front matter © 2011 Elsevier B.V. All rights reserved.
doi:10.1016/j.ijpharm.2011.05.025

mary particles with bond formation on contact surfaces (Duberg and Nyström, 1986). Compressibility is most often described by the change in the relationship between relative density, porosity, or volume and applied pressure represented by the Heckel (1961) and Walker (1923) models (Duberg and Nyström, 1986; Ilkka and Paronen, 1993; Paronen and Ilkka, 1996; Zupančič et al., 2008). In recent years the Walker model has received more attention in the study of pharmaceutical powder compressibility (Bacher et al., 2008; Ilić et al., 2009; Sonnergaard, 2000, 2006; Sovány et al., 2009).

Compactibility, on the other hand, can also be quantified in several different ways; most often it is expressed as the slope of the linear region of the tensile strength versus compression pressure (compactibility profile). The tensile strength of tablets defining powder compactibility can in some cases be correlated with the values K and w' of the Heckel and the Walker plot. Some studies have shown a relationship between the compressibility and compactibility of powders. Namely, well-compressible powders with high K or w' values are likely to generate many new contact points between the particles, which can lead to greater hardness and tensile strength of the compact (Sonnergaard, 2006).

There are many studies on the compression behavior of individual excipients and simple binary mixtures (Fichtner et al., 2007; Paronen, 1986; Patel et al., 2007, 2010; Roberts and Rowe, 1987; Sonnergaard, 1999, 2000; Yap et al., 2008) and the influence of preparation processes such as granulation on their compaction (Bacher et al., 2007, 2008; Freitag and Kleinebudde, 2003; Horisawa et al., 2000). According to the studies (Bacher et al., 2008) wet processed granules showed in general better compression properties. However, only a few published studies deal with the compression of complex but realistic mixtures that are produced for the market (Inghelbrecht and Remon, 1998; Zupančič et al., 2008). Especially interesting is the compression behavior of the same formulation produced using different technological procedures, such as wet and dry granulation or direct tableting on the production scale.

The purpose of this study was to investigate the effect of dry and wet granulation on particle size distribution and flow properties of the granules produced. It further aimed to evaluate compressibility and compactibility of dry granulated, wet granulated, and directly compressible mixtures and to compare the results. This was achieved using the Heckel and Walker models and analysis of compression energies in force–displacement curves; the results were compared. The quality of tablets produced was investigated with respect to friability and disintegration time in order to discover what the behavior of complex realistic mixtures used in tablet production is. Therefore, the same model placebo mixture was used throughout the study, either as a directly compressible mixture or by processing the powders using wet (high-shear and fluid-bed) or dry (roller compaction and slugging) granulation procedures.

2. Materials and methods

2.1. Materials

The model placebo mixture consisted of lactose monohydrate (filler, Pharmatose DCL15, DMV International GmbH), 65.42% (w/w); microcrystalline cellulose (filler/dry binder, MCC, Avicel PH 102, FMC International), 25.01% (w/w); sodium starch glycolate (disintegrating agent, Primojel, DMV International GmbH), 5.18% (w/w); polyvinylpyrrolidone (binder, Povidone K25, BASF SE), 3.31% (w/w); colloidal silica (lubricant, Aerosil 200, Evonik degussa GmbH), 0.36% (w/w); and magnesium stearate (antiadhesive agent, FACI SPA), 0.72% (w/w).

2.2. Preparation of tableting mixtures

Tableting mixtures were prepared according to the procedures enumerated and described below. Before preparation of the mixture, all materials were sieved manually through a sieve with a mesh size of 0.8 mm. The weighted amounts of powders were the same for all mixtures: lactose monohydrate (7.32 kg), microcrystalline cellulose (2.80 kg), Povidone K25 (370 g), and Primojel (580 g).

2.2.1. High-shear granulation (HSG)

Weighted powders were mixed with a high-shear mixer (Collette Ultima Gral TM 75, Collette, Wommelgem, Belgium) for 2 min at an impeller speed of 200 rpm. Purified water was sprayed with a spray rate of 0.7 kg/min at a constant impeller speed of 200 rpm until the motor power reached 1.1 kW. The total amount of granulation liquid used was 5.0 kg and the total spraying time was 410 s. After spraying, the granulate was kneaded for 120 s at an impeller speed of 305 rpm, without the chopper activated, until the motor power reached 2.3 kW. Wet granules were transferred to the fluid-bed dryer (Aeromatic TSG 2, GEA Aeromatic, Bubendorf, Switzerland) and dried at an inlet air T = 70–80 °C and air flow of 500 m^3/h. Drying lasted for 56 min until the exhaust air reached T = 41.5 °C. Dried granules were sieved (Quadro Comil U 10, Quadro Engineering, Waterloo, Ontario, Canada) using a sieve with a mesh size of 1.0 mm. The granules obtained were mixed with Aerosil 200 (37.2 g) in a 50 L biconical mixer (Iskra Pio, Šentjernej, Slovenia) at 20 rpm for 10 min. After the addition of Aerosil 200, magnesium stearate (74.4 g) was added and mixing was continued for 2 min at 10 rpm.

2.2.2. Fluid-bed granulation (FBG)

Weighted powders without Povidone were mixed in a fluid-bed granulator (Aeromatic TSG, 2 GEA Aeromatic, Bubendorf, Switzerland) at an inlet air T = 70 °C and air flow of 200 m^3/h. Mixing lasted 37 min until the exhaust air reached T = 37 °C. Then 5.37 kg of 6.89% (w/w) aqueous solution of Povidone K25 was sprayed at an inlet air T = 60 °C and the air flow was increased from a starting value of 250 m^3/h to 450 m^3/h by the end of the spray phase. The atomizing air pressure was 1.5 bar. Spraying of the granulation liquid lasted 14 min until the exhaust air reached T = 25.1 °C. Drying was performed for 52 min at an inlet air T = 60 °C; the air flow was decreased from a starting value of 450 m^3/h to 250 m^3/h at the end of drying phase, until an exhaust air T = 39.3 °C was reached. Dried granules were sieved and lubricated according to the procedure described in Section 2.2.1.

2.2.3. Dry granulation by roller compactor (DGRC)

Weighted powders were mixed in a 50 L biconical mixer (Iskra Pio, Šentjernej, Slovenia) at 20 rpm for 10 min. The powder mixture was compacted with a roller compactor (Chilsomator IR 220, Fitzpatrick, USA) using rolls 2 cm wide ($2R$ = 20 cm) using the following set parameters: roll pressure 20 bar, roll force 4.2 kN/cm, roll speed 4.0 rpm, gap width 1.8 mm, vertical precompression screw (VPS) speed 250 rpm, and horizontal feeding screw speed 21 rpm. The ribbons were crushed using an oscillating sieve with a 1.0 mm mesh size (Fitzmill L1A, Fitzpatrick, USA) at a mill speed of 1200 rpm. The obtained granules were sieved and lubricated according to the procedure described in Section 2.2.1.

2.2.4. Dry granulation by slugging (DGS)

Weighted powders with added Aerosil 200 (40 g) were mixed in a 50 L biconical mixer (Iskra Pio, Šentjernej, Slovenia) at 20 rpm for 10 min. Then magnesium stearate (80 g) was added and additional mixing was performed at 10 rpm for 2 min. Slugging was performed on a rotary tableting machine (Kilian T300/Vicon,