International Journal of Pharmaceutics 466 (2014) 266–275

Contents lists available at ScienceDirect

International Journal of Pharmaceutics

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

Compaction of functionalized calcium carbonate, a porous and crystalline microparticulate material with a lamellar surface

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ARTICLE INFO

Article history:
Received 31 January 2014
Received in revised form 7 March 2014
Accepted 9 March 2014
Available online 12 March 2014

Keywords:
Contact surface
Lamellar surface
Tensile strength
Mercury porosimetry
Leuenberger equation
Compaction behavior

ABSTRACT

In the present study, we aimed to characterize the compressibility and compactibility of the novel pharmaceutical excipient, functionalized calcium carbonate (FCC). We studied three FCC modifications and compared the values for compressibility and compactibility with mannitol, microcrystalline cellulose (MCC), and ground calcium carbonate (CC 330) as well as mixtures of paracetamol and MCC or FCC at drug loads of 0%, 25%, 50%, 75%, and 100% (w/w). We used Heckel analysis, modified Heckel analysis, and Leuenberger analysis to characterize the compaction and compression behavior of the mixtures. Compaction analysis of FCC showed this material to markedly differ from ground calcium carbonate, exhibiting properties, i.e. plastic deformability, similar to those of MCC. This effect was attributed to the highly lamellar structure of FCC particles whose thickness is of the order of a single crystal unit cell. According to Leuenberger parameters, we concluded that FCC-based tablet formulations had mechanical properties equal or superior to those formulated with MCC. FCC tablets with high tensile strength were obtained already at low compressive pressures. Owing to these favorable properties (i.e. marked tensile strength and porosity), FCC promises to be suitable for the preparation of solid dosage forms.

1. Introduction

In response to the introduction of the Process analytical technology Initiative by the Food and Drug Administration (FDA) and the Quality by Design (QbD) paradigm in pharmaceutical research and development, there is a need for novel, fully characterized multifunctional excipients for pharmaceutical products (FDA, 2004).

Compaction behavior, i.e. compressibility, compactibility, and pressure susceptibility, are critical criteria that need to be met to avoid issues in scale-up or stability of solid dosage forms. Performance of materials under pressure has been extensively studied, and the criteria known to account for compression and compaction behavior have been defined. These criteria are often used as composite assessment to determine the suitability of excipients for target formulations.

Compressibility of a material is the relationship between compaction pressure and tablet porosity (Leuenberger, 1982; Leuenberger and Jetzer, 1984). Several researchers suggested various equations to describe compressibility (Heckel, 1961a; Heckel, 1961b; Cooper and Eaton, 1962; Nelson et al., 1955). One of the approaches to analyze compaction behavior was proposed by Heckel. In the present work, data were analyzed according to the Heckel equation. It is a popular equation that allows to compare volume reductions among different materials under constant experimental conditions (York, 1979; Duberg and Nyström, 1986). The major advantage of the Heckel equation is the availability of a large reference dataset. This makes the Heckel equation a convenient tool for analysis and comparison of different materials. Heckel analysis assumes that the volume reduction (reduction of compact porosity) under pressure follows first-order kinetics (Heckel, 1961a; Heckel, 1961b). The reciprocal of the Heckel slope is defined as the yield pressure of the material and represents the resistance of a material to deformation (Hersey and Rees, 1971). Susceptibility of a material to pressure can be taken into account by the modified Heckel equation, which is particularly suitable for low pressure ranges (Kuentz and Leuenberger, 1999).

Powder compactibility is often assessed by plotting the crushing strength as a function of compressive pressure (Leuenberger, 1982;

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http://dx.doi.org/10.1016/j.ijpharm.2014.03.027
0378-5173/

Leuenberger and Jetzer, 1984). Nowadays, crushing strength is mostly replaced by tensile strength because tensile strength takes differences in tablet size into account (Fell and Newton, 1968). Jetzer et al. published an equation to calculate the compactibility and compression susceptibility. These two parameters provide information about the deformation of the material under stress and the bonding properties of the material (Jetzer et al., 1983).

The roller compaction process leads to the formation of secondary micro-hardened regions in the roller-compacted ribbons of materials, such as magnesium carbonate (Freitag et al., 2004). We assumed a similar behavior for highly lamellar materials, due to the formation of local hardening in zones consisting of interpenetrating or interlocking lamellae. According to this hypothesis, we assumed the contact surfaces to be a governing factor to achieve compacts of higher tensile strength even at lower pressures.

Functionalized calcium carbonate (FCC) is a particulate (5–15 μm in size) material with highly developed surface and internal structures. It is produced by re-precipitation of inorganic mixed salts (calcium phosphate in this case) incorporating the starting material (calcium carbonate) under controlled conditions to form microporous particles with a specific lamellar surface area of 40–80 m^2/g and a porosity of approximately 70%. In a previous study, we successfully used this substance to produce mechanically robust, orally dispersible tablets by direct compression (Stirnimann et al., 2013). In the present study, we characterized compressibility and compactibility of the novel pharmaceutical excipient FCC.

2. Materials and methods

2.1. Materials

Three different modifications of FCC (VP-OM2501 S01, VP-OM2501 S02, and VP-OM2501 S03, Omya International AG, Oftringen, Switzerland) were compared to microcrystalline cellulose (MCC SANAQ® 102, Pharmatrans Sanaq AG, Allschwil, Switzerland), calcium carbonate (PharMagnesia CC Type Natura 330, Lehmann & Voss & Co., Hamburg, Germany), and mannitol (Mannitolum Ph Eur, Hänseler AG, Herisau, Switzerland). As an active pharmaceutical ingredient, we chose paracetamol (Acetaminophen USP/Paracetamol Ph Eur Powder, Mallinckrodt, Saint Louis, MO, USA).

Hydroxypropyl methyl cellulose (HPMC) E5PLV (Colorcon Limited, Dartford Kent, UK) was used as a binder for wet granulation. Magnesium stearate (Novartis, Basel, Switzerland) was used as a lubricant for tableting. For particle-size distribution measurements, we used isopropyl myristate (Hänseler) as a dispersant. Mercury (Sigma-Aldrich, Munich, Germany) was used as a non-wetting liquid for porosimetry measurements.

2.2. Methods

2.2.1. Characterization of raw materials

Scanning electron microscopy (SEM) images were obtained using an FEI/Philips XL30 FEG instrument (Philips, Eindhoven, Netherlands). The samples were sputtered with a 40 nm gold layer by a sputter coating device (MED 020, BalTec, Balzers, Liechtenstein) before microscope imaging.

Apparent true densities of the substances were determined by helium pycnometry (Micromeritics AccuPyc 1330, Norcross, GA, USA). Before the measurement, substances were dried overnight (12–15 h) under nitrogen flow in a vacuum drying cabinet type KVTS 11 (Salvis, Oftringen, Switzerland).

Particle-size distribution was determined with the Mastersizer X long bed laser diffractometer (Malvern Instruments, Malvern, Worcestershire, UK). FCC, MCC, CC 330, and paracetamol were dispersed in isopropyl myristate and analyzed by using the small volume sample presentation unit (Malvern Instruments). For mannitol, we used a dry powder feeder (Malvern Instruments). Measurements were performed in triplicate.

A Nova 2000e (Quantachrome Instruments, Boynton Beach, FL, USA) was used to quantify the specific surface area of FCC with the five-point BET (Brunauer–Emmett–Teller) method. After degassing the samples for 12–15 h at room temperature, they were measured in duplicates with nitrogen at constant temperature (77.4 K). Mannitol, MCC, CC 330, and paracetamol were not assessed due to the limit of resolution of the instrument (<0.01 m^2/g).

Pore-size distribution of the substances was determined with an Auto Pore IV 9500 mercury porosimeter (Micromeritics Instrument, Norcross, GA, USA). Low-pressure mercury intrusion ranged from 3.59 kPa to 206.64 kPa. During high-pressure mercury intrusion, the pressure ranged from 206.64 kPa to 206.78 MPa. For both high- and low-pressure intrusion, equilibration time was set to 10 s.

2.2.2. Granulation of FCC

Granulation of FCC was achieved by roller compaction (Chilsonator IR220 roller compactor, Fitzpatrick, Elmhurst, IL, USA). The roll pressure was set to 20 bars at a roll gap of 1 mm and a roll speed of 4 rpm. The speed of the horizontal feed screw was set to 25 rpm, and the vertical feed screw moved with a speed of 120 rpm. To ensure constant powder flow to the horizontal feeding screw within the powder chute, we used a stirring device of type RE162 (IKA Labortechnik, Janke & Kunkel GmbH & Co. KG, Staufen, Germany) at 35 rpm. High-shear mixer granulation of FCC was carried out with an Oystar Micromix high-shear mixer (Hüttlin GmbH, Schopfheim, Germany). The binder (HPMC E5PLV) was dissolved in distilled water using a magnetic stirrer IKAMAG® RCT (IKA Labortechnik, Janke & Kunkel Gmbh & Co. KG) to obtain a 4% (w/w) solution. The binder solution was foamed with pressurized air (approximately 8 bars) in a Tornador® Z-011 foam gun (Bendel Werkzeuge, Bad Bevensen, Germany). FCC S02 was granulated with 5% (w/w) HPMC E5PLV. The foamed binder was added to the powder at a speed of 5.3 g/min with a peristaltic pump (Vario-Pumpsystem-Antrieb, Ismatec SA, Glattbrugg, Switzerland). The impeller speed was approximately 150 rpm and the chopper speed was approximately 1500 rpm. Afterwards, the granules were dried at 60 °C in a Heraeus UT 6200 drying oven (Sorvall Heraeus Instruments, Hanau, Germany) until loss on drying (LOD) was approximately 2%. LOD was determined gravimetrically with a Mettler LP 16 infrared lamp and a Mettler PE 360 balance (Mettler Instruments, Greifensee, Switzerland).

After roller compaction and high-shear granulation, ribbons and granules were milled with a Fitz®Mill comminutor L1A (Fitzpatrick) at a speed of approximately 500 rpm. Granules were sieved for 10 min at an amplitude setting of 46 to obtain particles sized between 180 μm and 500 μm (Retsch Vibro, Schieritz & Hauenstein AG, Arlesheim, Switzerland).

2.2.3. Tablet preparation

Prior to compaction, each powder was sieved through a 1000 μm sieve to eliminate agglomerates. Powders and granules were dried overnight (12–15 h) under nitrogen flow in a vacuum drying cabinet of type KVTS 11 (Salvis).

Mixtures were prepared by blending excipients with paracetamol to obtain paracetamol contents of 25% (w/w), 50% (w/w), 75% (w/w), and 100% (w/w). Furthermore, a reference formulation without paracetamol was prepared. Powders were mixed for 10 min in a tumbling mixer (Turbula T2C, Basel, Switzerland) at 32 rpm.

All powders and granules were compressed using a Styl'One 105 mL tablet press (Medel'Pharm, Beynost, France) with 10 mm round flat tooling. Analis software version 2.01 (Medel'Pharm) was used to operate the instrument and monitor the process. Due to the highly variable porosities of the raw materials, tablets with varying porosities were obtained at defined pressure. Therefore, we decided to hold the tablet volume constant at the lowest compressive