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Powder compression mechanics of spray-dried lactose nanocomposites

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ABSTRACT

The aim of this study was to investigate the structural impact of the nanofiller incorporation on the powder compression mechanics of spray-dried lactose. The lactose was co-spray-dried with three different nanofillers, that is, cellulose nanocrystals, sodium montmorillonite and fumed silica, which led to lower micron-sized nanocomposite particles with varying structure and morphology. The powder compression mechanics of the nanocomposites and physical mixtures of the neat spray-dried components were evaluated by a rational evaluation method with compression analysis as a tool, using the Kawakita equation and the Shapiro–Konopicky–Heckel equation. Particle rearrangement dominated the initial compression profiles due to the small particle size of the materials. The strong contribution of particle rearrangement in the materials with fumed silica continued throughout the whole compression profile, which prohibited an in-depth material characterization. However, the lactose/cellulose nanocrystals and the lactose/sodium montmorillonite nanocomposites demonstrated high yield pressure compared with the physical mixtures indicating increased particle hardness upon composite formation. This increase has likely to do with a reinforcement of the nanocomposite particles by skeleton formation of the nanoparticles. In summary, the rational evaluation of mechanical properties done by applying powder compression analysis proved to be a valuable tool for mechanical evaluation for this type of spray-dried composite materials, unless they demonstrate particle rearrangement throughout the whole compression profile.

1. Introduction

We have in a series of papers studied nanocomposites of co-spray-dried lactose and nanofillers (Hellrup et al., 2015, 2016; Hellrup and Mahlin, 2017). The lactose has been compounded with three different nanofillers, that is, fumed silica (A200), cellulose nanocrystals (CNC), and sodium montmorillonite (Na-MMT). The general aim with these studies has been to create novel functional materials of pharmaceutical relevance with improved properties such as physical stability and hygroscopicity. Lactose, one of the most commonly used pharmaceutical excipients, is easily transformed into an amorphous powder by spray-drying. The formed material rapidly recrystallizes upon humidity exposure but the physical stability of the amorphous lactose improves significantly when formulated into nanocomposites with high nanofiller content (Hellrup et al., 2015; Hellrup and Mahlin, 2017). Lactose/CNC and lactose/Na-MMT nanocomposites with 80% nanofiller have shown to be physically stable for months under humidity stressed conditions (Hellrup and Mahlin, 2017).

Along with physical stability and hygroscopicity, knowledge on the mechanical properties of lactose is of great interest (Armstrong, 1997). Lactose, in the form of α-lactose monohydrate and spray-dried lactose, is one of the most frequently used excipients due to low cost and reasonable compaction characteristics (Lerk, 1993). Up till now, mechanical properties of the nanocomposites of lactose with Na-MMT, A200 and CNC have not been studied. Polymer nanocomposites, which structurally are very similar materials, have attracted considerable interest in the polymer research area due to strong influence on material properties of the polymers upon nanofiller incorporation. Among other, polymer nanocomposites may possess superior mechanical properties

Abbreviations: ρ, density; ρ_{app}, apparent density; ρ_{bulk}, bulk density; A200, fumed silica Aerosil® 200 Pharma; C, engineering strain; CNC, cellulose nanocrystals; $d_{50\%}$, median particle diameter; E, porosity of the compact; E_0, initial porosity of the powder bed; f, Shapiro compression parameter; Na-MMT, sodium montmorillonite; P, compaction pressure; P_y, yield pressure; SKH, Shapiro–Konopicky–Heckel; V, volume of the powder column at pressure *P*; V_0, initial powder volume; *w*, weight fraction.

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compared with neat polymers (Jordan et al., 2005; Majeed et al., 2013; Sinha Ray and Okamoto, 2003). In this context, it is of interest to study the mechanical properties of the lactose based nanocomposites.

Three well established approaches to gain information about mechanical properties are uniaxial confined compression, testing of compacts with for instance indentation and bending tests, and testing of single particles (Katz and Buckner, 2013; Olusanmi et al., 2011; Ray and Rowe, 1996; Yap et al., 2008). Compression analysis, that is, uniaxial confined compression, is a method that yields information about mechanical properties from a large number of analyzed particles of an investigated powder, but still with low material consumption (Nordström et al., 2012). It is especially attractive for materials with small particle size and/or materials that are demonstrating capping or laminating tendencies, since such materials are hard to convert into compacts for analysis by other methods. Nordström et al. (2012) have developed a standardized protocol for evaluation of powder mechanical properties, to describe and distinguish between powders regarding their compression behavior. In this protocol, the compression profile is described in terms of a pressure–engineering strain relationship, using the Kawakita equation (Kawakita and Lüdde, 1971), and a porosity–pressure relationship, using the Shapiro–Konopicky–Heckel (SKH) equation (Heckel, 1961). This protocol was in this study applied to distinguish mechanical properties of the nanocomposites depending of composition of the nanocomposites.

In our studies of the pharmaceutical nanocomposites with lactose we have strived at getting an understanding of structure–dynamics–functionality relationships of the materials with regards to pharmaceutical relevant properties such as physical stability (Hellrup et al., 2015, 2016; Hellrup and Mahlin, 2017). The applied nanoparticles have different shape and surface properties. CNC, which in the literature also is referred to as cellulose whiskers, are rod shaped. A200 consists of close to spherical silica nanoparticles. MMT, the main constituent of bentonite, consists of clay mineral particles made up of stacked MMT sheets into a layered structure that enable intercalation of other substances in the MMT interlayer space (Bergaya and Lagaly, 2013; Hellrup et al., 2016; Holmboe et al., 2012; Sinha Ray and Okamoto, 2003), for instance lactose (Hellrup et al., 2016). Independently of nanofiller type, the lactose forms a continuous phase at low nanofiller contents in the nanocomposites. But at sufficiently high nanofiller contents the lactose is present in nano-sized extra-particular voids (Hellrup et al., 2015, 2016; Hellrup and Mahlin, 2017).

The aim of this study was to study the structural impact on the powder compression mechanics, by a rational evaluation with compression analysis as a tool, of co-spray-dried lactose/nanofiller nanocomposites with varying structure and morphology. The structural variation was achieved by varying the lactose–nanofiller composition of three nanofillers with different shape and surface properties in the nanocomposites.

2. Material and methods

2.1. Materials

Alpha-lactose monohydrate (Ph. Eur., Fluka Analytical, Sigma-Aldrich, Buchs, Germany) was used to prepare 15 wt% solutions using de-ionized water. Sodium montmorillonite, Cloisite® Na^+ (Na-MMT), kindly provided by BYK Additives & Instruments (Wesel, Germany), fumed silica, Aerosil® 200 Pharma (A200), a gift from Evonik (Essen, Germany), and cellulose nanocrystals (CNC) (University of Maine Process Development Center, Orono, ME, USA), were used as nanofillers.

2.2. Sample preparation

Na-MMT (5 wt%) was dispersed by sonicating it in water with a ultrasonic bath (Branson 5210, Soest, Netherlands) for 1 h and then stirred for 18 h in room temperature followed by 4 h in a water bath at 80 °C. CNC and A200 (5 wt%) was dispersed by sonication with water using a VC 750 ultrasound processor equipped with a 13 mm standard probe with threaded end and replaceable tip (Sonics & Materials, Inc., Newtown, CT). The suspensions were sonicated for 20 min with 100% amplitude in a glass beaker which was cooled in ice water. The suspensions were then centrifuged at 615*g* for 30 min to remove metal filings from the ultrasound probe. The centrifugations were done in an F0685 rotor in a Beckman Avanti 30 compact centrifuge (Palo Alto, CA). The suspensions were mixed with water and lactose solution (15 wt%), that had equilibrated with regard to spontaneous mutarotation, in proportions leading to a combined fraction dry material (nanofillers + lactose) of 6.5 wt % and 0–100 wt% Na-MMT, A200, or CNC, respectively, in lactose.

The prepared suspensions were spray-dried with a Mini Spray Dryer B-290 (Büchi, Flawil, Switzerland). A nozzle tip of 0.7 mm and nozzle screw cap of a diameter of 1.5 mm were used. The spray-dryer was operated in an open mode, whereby the drying gas was passed through a filter and a dehumidifier (B-296) before entering the drying chamber. A high-performance cyclone was used. Standardized spray-drying settings were used during the spray-drying; volume flow, nozzle cleaning, inlet temperature, spray air flow, and feed rate were set at 38 m^3/h, level 2, 150 °C, 473 l/h, and 4 ml/min respectively.

Physical mixtures of lactose and the nanofillers were prepared in batches of 3 g by geometric diluting (triturating) neat spray-dried lactose and neat spray-dried nanofillers using a mortar and pestle.

2.3. Characterization of powers

The apparent densities (ρ_{app}) of the samples were determined with a helium pycnometer (AccuPyc 1330, MicroMeritics, Londonderry, NH, USA). Each sample was measured three times with ten cycles for each experiment. The ρ_{app} for the physical mixtures was determined according to

$$\rho_{app} = \frac{w_1 + w_2}{\frac{w_1}{\rho_1} + {w_2}/{\rho_2}} \quad (1)$$

where w_1 and w_2 are the weight fractions of the neat spray-dried components, and ρ_1 and ρ_2 denote the corresponding apparent densities.

The bulk density (ρ_{bulk}) was measured by gentle pouring of the sample into a cylinder (diameter 11.42 mm and height 150 mm) and the height was recorded (Mitutoyo Digimatic, ID-C, Tokyo, Japan) (n = 3). The ρ_{bulk} measurements were performed to mimic the conditions in the die during loading and were used to calculate the approximate initial volumes of the powders in the die during the powder compression.

Particle size, shape, and surface morphology were examined with scanning electron microscopy. The samples were coated by sputter coating for 120 s at 2 kV with gold using a Polaron SC7640 sputter coater (Quorum Technologies Ltd, Newhaven, UK) and then imaged using a LEO 1550 (Zeiss, Oberkochen, Germany) operated at 2.0 kV.

The particle median diameter of the spray-dried powders was determined using a laser light scattering particle size analyzer (SALD 7500 nano, Shimadzu, Japan). Approximately 25 mg of the powders were ultrasonicated in 500 μl 1% docusate sodium in heptane solution at 30% effect for 5 min with a Bandelin Ultrasonic Homogenizer HD 3200 with a cup horn BB6 for indirect sonication.