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The effect of the drying temperature on the properties of wet-extruded calcium stearate pellets: Pellet microstructure, drug distribution, solid state and drug dissolution

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ABSTRACT

Although drying is widely applied during the manufacturing of solid dosage forms, its potential effect on the product's (key) properties is often underestimated. Hence, the present study addresses drying related modifications of wet-extruded pellets comprising calcium stearate (CaSt, matrix former) and ibuprofen (model drug). After spheronization, the pellets were tray dried at different temperatures. The dried pellets were evaluated regarding their microstructure, the ibuprofen distribution, solid state modifications and the resulting in-vitro dissolution profiles. The ibuprofen distribution profiles along the pellets' cross-sections varied for the different drying conditions. The profiles turned from inhomogeneous to uniform with increasing drying temperature. Temperatures above 20 °C yielded solid state modifications, including ibuprofen transition into the amorphous state and the formation of eutectic compositions. As none of the batches exhibited a high specific surface area associated with an open, well-interconnected pore system, the dissolution profiles were a function of the ibuprofen distribution. Differences in the solid state did not contribute to the dissolution behavior, since the CaSt matrix did not swell or dissolve in the dissolution medium. These findings show that drying may considerably affect the final product properties even for moderate drying conditions.

1. Introduction

Drying operations are often encountered during the manufacturing of solid pharmaceutical products. Frequently, its purpose is to remove any liquid, which was added for processing reasons. For example, during wet granulation processes, the formation of micro-particulate systems is only possible due to the addition of liquid. This liquid needs to be removed in a final processing step. Thereby, permanent solid bridges between the primary particles are formed (Farber et al., 2003), segregation and stability issues of the product are avoided and further processing is facilitated.

The wet extrusion/spheronization process is another technique to manufacture micro-particles. Similar to other wet granulation techniques, the liquid is finally removed during drying. However, drying does not only remove the liquid, but may modify the micro-particles', so-called pellets', properties. First, drying potentially affects the microstructure of the pellets (Baert et al., 1993; Balaxi et al., 2009; Bashaiwoldu et al., 2004b; Berggren and Alderborn, 2001b; Gómez-Carracedo et al., 2007), as materials that swell in the granulation liquid and shrink to a certain extent upon drying are frequently used as matrix materials (Berggren and Alderborn, 2001a; Fielden et al., 1992; Kleinebudde, 1994; Schrank et al., 2012, 2013). Hence, characteristics associated with the pellet micro-structure, including the in-vitro dissolution characteristics (Dyer et al., 1994; Gómez-Carracedo et al., 2007, 2008; Lutchman et al.,

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2005; Schrank et al., 2012, 2013; Sousa et al., 1996; Wlosnewski et al., 2010), the compaction behavior (Bashaiwoldu et al., 2004a,b, b; Berggren and Alderborn, 2001b; Gómez-Carracedo et al., 2008; Murray et al., 2007) and the mechanical strength (Schrank et al., 2012; Wlosnewski et al., 2010) were shown to be a function of the drying process conditions. Second, drying alters the physicochemical properties of the active pharmaceutical ingredient (API) after it is dissolved in the granulation liquid. Drying induced modifications of the API were reported with respect to solid state transitions (Herman et al., 1989; Sandler et al., 2005; Schrank et al., 2014; Yano and Kleinebudde, 2010) after re-crystallization and API re-distribution throughout the pellets (i.e., the API profile) due to intra-particular migration (Schrank et al., 2014). Polymorphic transitions affect the in-vitro dissolution behavior (Debnath and Suryanarayanan, 2004; Phadnis and Suryanarayanan, 1997; Yano and Kleinebudde, 2010). API accumulation at certain pellet regions was observed to alter the pellet's mechanical properties (Poutiainen et al., 2012) and the in-vitro dissolution characteristics (Huang and Brazel, 2001).

In general, a drying process can be subdivided into three stages according to the observed drying rate: (i) the pre-heating period, (ii) the constant-rate period (CRP) and (iii) the falling-rate period (FRP). During the pre-heating period the wet pellet surface temperature steadily increases yielding gradually increasing evaporation rates. During the CRP the pellet surface temperature is constant (i.e., the wet bulb temperature), since the energy loss due to evaporation and the heating rate are in equilibrium. The rate of evaporation does not change as long as the pellet surface is kept saturated due to capillary liquid flow from the pellet's interior toward the surface. At a certain point, however, the moisture content inside the pellet drops below a critical value indicating the start of the FRP, where the surface is not saturated anymore. The liquid recedes into the pellet, yielding a steady reduction of the drying rate. The liquid evaporates inside the pores and the rate of evaporation is governed by the vapor removal through the porous system via diffusion. Dry patches appear at or close to the pellet surface, at which the temperature gradually approaches the temperature of the surrounding drying medium (most often air).

The CRP is associated with uniform pellet shrinkage, leaving decreased pellet diameters and/or modified pore structures. The FRP does not induce changes with respect to the pellet diameter. Still, the inner pore structure may be changed in terms of pore size distributions (Schrank et al., 2013).

During the CRP dissolved API is transported with the convective liquid flow toward the pellets surface. The convective flow is more pronounced for a high permeability (Lekhal et al., 2001), which is governed by the microstructure, i.e., the pore size distribution, pore shape, pore connectivity and pore tortuosity (Liu et al., 2008). Once a supersaturated solution is created due to liquid evaporation, the API re-crystallizes at the pellet surface. API enriched shells are formed, while the pellet's interior is depleted of API. Alternatively, dissolved API may be transported back toward the center by diffusion driven by the concentration gradient that was formed over the pellet's cross-section. As a consequence, the API profile becomes uniform again or the API may even accumulate at the pellet's center. The final concentration profile is determined by the complex interplay of convection, diffusion, re-crystallization thermodynamics and the heat and mass transfer in the film around the pellet.

Migration of the API toward the pellet surface is prevented during the FRP. Instead, back-diffusion may become dominant and the API can accumulate in the pellet's center. For very harsh drying conditions (typically no CPR is observed) drug migration is even impeded. Here, convective flow toward the surface is suppressed and hence, no concentration gradient causing diffusion is formed. Moreover, film breakage occurs (Komiyama et al., 1980) (i.e., disruption of the formerly continuous liquid phase). Thereby, isolated liquid domains are formed suppressing API migration.

The present study investigates tray drying of pellets produced using wet extrusion/spheronization. In our previous work pellets were dried at 20 and 50 °C and the ibuprofen distribution profiles and solid state modifications were evaluated (Schrank et al., 2014). In the present study pellets were dried at different temperatures (i.e., 30, 40 and 60 °C) and the ibuprofen distribution and its solid state were investigated. Additionally, the pellet microstructure and the in-vitro dissolution profiles were determined for all drying temperatures (i.e., 20, 30, 40, 50 and 60 °C). Thereby, we aimed at generating a deep understanding of the effect of the drying temperature on: (i) the pellet microstructure, (ii) the spatial ibuprofen distribution, (iii) the solid state of ibuprofen and (iv) the corresponding in-vitro dissolution performance.

2. Materials and methods

2.1. Materials

Vegetable calcium stearate (CaSt) was purchased from Werba-Chem GmbH, Vienna, Austria. Ibuprofen (G.L. Pharma, Lannach, Austria) served as a model API and 96 v% ethanol (Merck, Darmstadt, Germany) was used as granulation liquid. Monopotassium phosphate and sodium hydroxide (both Merck, Darmstadt, Germany) served for dissolution medium preparation. Milli-Q water (ultrapure water according to ISO 3696), triethylamine, orthophosphoric acid 85%, and acetonitrile (all Merck, Darmstadt, Germany) were used as mobile phase during the HPLC measurements.

2.2. Pellet preparation and drying

Pellets containing 15 w% ibuprofen and CaSt as matrix material were prepared via wet extrusion/spheronization according to Schrank et al. (2014). In contrast to conventional extrusion processes, where the API is added as powder, ibuprofen was dissolved in the granulation liquid, i.e., ethanol. Thereby, a large fraction of ibuprofen stayed in the dissolved state throughout the entire preparation process and the impact of drying on the API's physicochemical properties could readily be studied. In the previous study tray drying was performed at 20 and 50 °C (Schrank et al., 2014). During the present study pellets were dried at 30, 40, and 60 °C and at a relative humidity ranging between 25 and 35%. Immediately after spheronization, the pellets were transferred into round, flat-bottom bowls with a diameter of 17 cm equaling a pellet bed surface are of 227 cm^2. The bed height was 8 mm, which results in approximately 6 pellets lying on top of each other. Drying was carried out until a constant weight was reached.

The drying curves were determined by weighing the pellets after certain time intervals and the moisture content was calculated as a function of time. For each drying temperature three batches were prepared.

2.3. Pellet characterization

The pellets were sieved according to Ph. Eu. 7.0 2.9.38 and the fraction between 1.4 and 1.8 mm was used for characterization studies.

2.3.1. Differential scanning calorimetry (DSC)

DSC measurements were conducted using a DSC 204 F1 Phoenix (Netzsch, Selb, Germany). Pellets (sample weight 5–10 mg) were gently crushed with a spatula and transferred into aluminum pans that were closed with a pierced lid via cold welding. Samples were heated from 20 to 100 °C with a heating rate of 5 K/min. The