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Improvement of mechanical properties of pellet containing tablets by thermal treatment

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ABSTRACT

Batches of partially spray-dried lactose tablets with three different initial tensile strength (~20 N, ~35 N, ~50 N) were made. Changes along a 24 h long thermal treatment at 100 °C in tensile strength, friability, individual mass, water content, disintegration time, average free volume and wetting properties were evaluated. Caffeine containing gastroresistant pellets were gained by drug layering and filmcoating of inert microcrystalline cellulose pellet cores in fluid bed equipment. Shape, size, mechanical properties, drug content and dissolution profile of the coated pellets were determined. Batches of pellet containing tablets with three different pellet-filler ratios were compressed where partially spray-dried lactose was used as a filler-binder material.Characteristics of pellet containing tablets were evaluated before and after a 24 h long thermal treatment at 100 °C. Results shown that the poor initial mechanical properties (friability, tensile strength) were improved by thermal exposure while there were no remarkable alterations in drug release profiles.

1. Introduction

The tablet compression may be followed in some cases by further technological steps during which tablets are exposed to unconventionally high temperatures. Examples of this kind of procedures are drying of lyophilized or wet compressed tablets (Yunxia et al., 1999; Sugimoto et al., 2005), thermal curing of the filmcoated tablets (Yuasa et al., 2000; Gendre et al., 2012) or preparation of orally disintegrating tablets based on phase transition (Kuno et al., 2005).

The changes of mechanical properties of tablets caused by thermal exposure have been studied and evaluated during the recent decades. There are two different yet related approach to describe the theoretical background of the hardness increase phenomenon.

According to the first theory, the hardness increase is caused by the amorphous-crystalline transition of the filler-binder materials (Tesfai et al., 1994; Alderborn and Ahlneck, 1991; Ahlneck and Zografi, 1990). Exceeding the glass transition temperature of the given material makes possible the solid phase crystallization of the amorphous portion of the excipient (Roos and Karel, 1992). A certain amount of amorphous material in the powder blend prior to tabletting is a necessary condition of this mechanism.

The second approach states that the hardness increase is induced by the initial water content of the powder blend. The water soluble excipient and the water forms saturated solutions inside the tablet matrix structure and leaves new solid bonding surfaces behind upon heating and water evaporation (Chowan, 1980).

In case the filler-binder blends initial water content is relatively high and it contains water soluble material and an amorphous portion as well the hardness increase of the compressed tablets can occure by heating due to both mechanism described above.

During the development and manufacturing of pellet containing tablets the compression force is among the crucial technical variables especially in case the modified release of the active pharmaceutical ingredient from the tablet is based on coated individual pellets. Relatively high compression pressures lead to the fracture or thinning of the polymer coating thus to the alteration of the initial dissolution profile of the uncompressed pellets (Bodmeier, 1997; Shajahan et al., 2010). On the other hand, lower compression force may result in tablets with unsatisfactory mechanical properties like low tensile strength and high friability.

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There have been several attempts to diminish the coating fracture phenomenon occurring along tablet compression such as application of cushion layered pellets (Hosseini et al., 2013), co-granulation process (Xin et al., 2013) or coating agent mixtures with enhanced elastic properties (Abbaspour et al., 2008; Rujivipat and Bodmeier, 2012).

The aim of the present study was to assess altering physical and physico-chemical properties of tablets made of spray-dried lactose with three different initial tensile strength along a 24 h long 100 °C thermal treatment process. Changes in tensile strength, friability, individual mass, water content, disintegration time, average free volume and wetting properties were evaluated. The spray-dried lactose (Flowlac® 100) with an average amorphous content of 15% and an initial water content of 5.02 ± 0.81% was chosen because of its exceptional hardening capability.

Based on the results of evaluation of changes in mechanical properties the further purpose of the study was to investigate whether it is possible to prepare a modified release pellet containing tablet and improve the initial poor mechanical features of the tablet by thermal treatment without altering the original dissolution profile.

2. Materials and methods

2.1. Materials

Ethispheres® 600 microcrystalline cellulose (MCC) pellet cores were purchased from NP Pharm Pharmaceuticals (Bazainville, France). Pharmacoat® 606 (HPMC) was supplied by Shin-Etsu Chemical Co. (Tokyo, Japan), dispersion of acrylate based coating agent Eudragit® L30D-55 by Evonik Industries AG (Darmstadt, Germany), Sunset Yellow® FCF food colour by Sensient Food Colors UK (Norfolk, United Kingdom), triethyl-citrate and micronized talc by Sigma–Aldrich Co. (Taufkirchen, Germany). Spray-dried lactose for direct compression Flowlac® 100 with an average 15% of amorphous lactose and with 5.02 ± 0.81% of initial water content was obtained from Meggle Pharma (Wasserburg, Germany). Caffeine, hydrochloric acid solution, sodium hydroxide and potassium dihydrogen phosphate were produced by Molar Chemicals (Budapest, Hungary). Purified water was gained using a Christ Ministil® P-24 ion exchange column (Ovivo Water, Wolverhampton, United Kingdom).

2.2. Methods

2.2.1. Preparation of caffeine containing sustained release pellets

Batch of 200 g inert MCC pellet cores were layered and filmcoated in an Aeromatic STREA 1 fluid-bed equipment (Aeromatic Fielder AG, Bubendorf, Switzerland). The 400 g of aqueous layering solution containing 8 g HPMC, 20 g caffeine and 0.4 g Sunset Yellow was sprayed onto the cores by bottom-spraying. During the process, the liquid was stirred and tempered (at about 55–60 °C) continuously to keep the drug in solution. The set parameters were the following during the layering process: inlet air flow rate: 80–130 m^3/h, inlet air temperature: 50 °C, outlet air temperature: 37–40 °C, atomizing pressure 1 bar, spray rate: 5–6 g/min, nozzle diameter: 0.8 mm. The layered pellets were dried for 10 min at 50 °C. The aqueous coating dispersion contained 84 g of Eudragit® L30D-55, 2.6 g of triethyl-citrate plasticizer, 12.6 g of micronized talc as antistatic agent and 103 g of purified water. The dispersion was gently stirred continuously during the coating process to prevent sedimentation of the talc. The coating conditions were: inlet air flow rate: 80 m^3/h, inlet air temperature: 45 °C, outlet air temperature: 31–34 °C, atomizing pressure 1 bar, spray rate: 4-5 g/min, nozzle diameter: 0.8 mm. The coated pellets were dried for 10 min at 45 °C.

2.2.2. Preparation of pellet-free lactose based matrix tablets

The 600 mg pellet-free lactose based matrix tablets consisted of 99%w/w of Flowlac® 100 and 1%w/w of magnesium stearate as lubricant. The homogenious powder blend was compressed on a single punch tablet press (Fette Exacta 1, Fette Compacting GmbH, Schwarzenbek, Germany) equipped with flat-faced, bevelled-edged punches with a diameter of 14 mm. The compression force was adjusted to obtain tablets with the desired tensile strength (Hardness 1 ≈20 N, Hardness 2 ≈35 N and Hardness 3 ≈50 N).

2.2.3. Preparation of lactose based multiple unit systems

Different ratios of drug loaded, enteric coated pellets and Flowlac® 100 powder blend (containing 1% w/w of magnesium stearate) were compressed using the tablet-press described above. The three different types of MUPSs (multiple unit pellet systems) consisted of 200 mg of drug layered, coated pellets and 400 mg of Flowlac® 100 powder blend (Sample P1), 250 mg of pellets and 350 mg of Flowlac® 100 powder blend (Sample P2) and 300 mg of pellets and 300 mg of Flowlac® 100 powder blend (Sample P3), respectively. The coated pellet/powder blend for each individual tablet was prepared by manually mixing the coated pellets with lubricated Flowlac® 100 in Eppendorf tubes for 20 s and filled into the die of tablet press. The compression force was set to gain tablets with the highest tensile strength possible.

2.2.4. The thermal treatment process of enteric coated pellets and tablets

The process was carried out in a Labor-Innova drying chamber (Labor-Innova Kft., Budapest, Hungary) at 100 °C. Coated pellets or

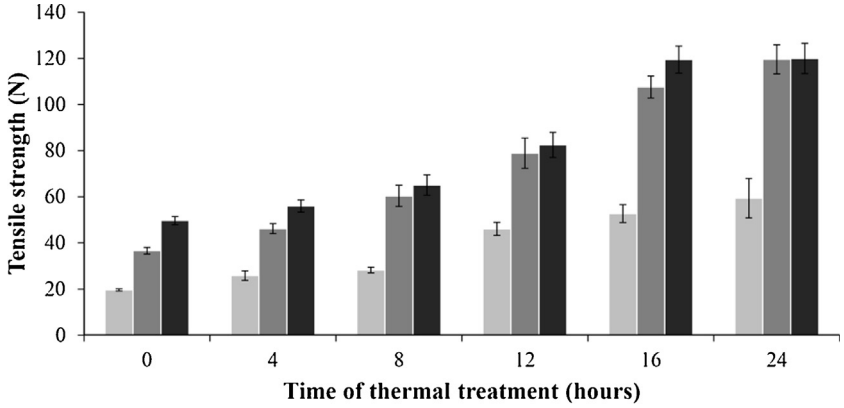

Fig. 1. Changes in tensile strength (N) of lactose tablets along thermal treatment at 100 °C (n = 10). Hardness 1; Hardness 2; Hardness 3.

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