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Improving the granule strength of roller-compacted ibuprofen sodium for hot-melt coating processing

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ABSTRACT

Solvent-free hot-melt coating processing is a novel and cost-efficient approach to manufacturing taste-masked multiparticulate systems. However, most API powders are fine and cohesive and not processable by hot-melt coating. The aim of this study was to produce dense and abrasion-resistant granules with high drug content (>80%) via roller compaction for hot-melt coating process optimization. The selected API was ibuprofen sodium dihydrate, a salt of ibuprofen with improved bioavailability and poor intrinsic compactibility.

The formulation and roller compaction process were developed for the production of granules with 94%$_{w/w}$ of API and low friability (~30%), using sorbitol and isomalt as excipients. The strong bonding mechanism relied on powder jamming prior to the rollers and was investigated via scanning electron microscopy, differential scanning calorimetry and small and wide angle X-ray scattering. It was shown that sorbitol crystals are solubilized during roller compaction and recrystallize as sorbitol hydrate, acting as strong solid bridges. The robustness of the roller compaction process and the re-compaction of fines were investigated. A statistical design of experiments was conducted to evaluate the hot-melt coating process for taste masking of ibuprofen sodium granules. Taste masking required coating ratios higher than 40%$_{w/w}$ of granule batch, emphasizing the need for high-drug-content and abrasion-resistant granules.

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1. Introduction

Ibuprofen sodium dihydrate (ibuprofen sodium) is a fast-acting salt of ibuprofen free acid and one of the most widely used nonsteroidal anti-inflammatory drugs today (Rainsford, 2009; Soergel et al., 2005). This sodium salt modification of ibuprofen was reported to be absorbed into plasma more rapidly than conventional ibuprofen and to have comparable tolerability and safety profile (Soergel et al., 2005). A multiparticulate drug delivery system, such as “direct to mouth” granules of ibuprofen sodium, would facilitate the swallowability for geriatric or pediatric population patients suffering from dysphagia (Gandhi and Baheti, 2013; Patel and Dhake, 2011; Patwekar and Baramade, 2012; Sharma and Chaurasia, 2013; Stegemann et al., 2011; Wahlich et al., 2013).

A “direct to mouth” system containing ibuprofen sodium must be taste-masked due to the two major taste components of ibuprofen: bitterness and burning sensation (Higton, 1999). Recently, our group presented a novel and cost-efficient approach to manufacturing a taste-masked multiparticulate system with a stable immediate release profile by applying lipid-based excipients in a solvent-free hot-melt coating process (Becker et al., 2013, 2016). This technique uses fluid bed technology to apply molten coating material into fluidized particles (Jozwiakowski et al., 1990; Jannin and Cuppok 2013; Lopes et al., 2015). The re-solidification of molten material on the surface of particles creates the coating layer. However, hot-melt coating cannot be applied to commercially available ibuprofen sodium that has small particle size (<100 μm), low bulk density (<0.5 g/ml) and dusty properties (Jannin and Cuppok, 2013; Jozwiakowski et al., 1990; Werner et al., 2007). Since these characteristics are common to the majority of APIs, a granulation step is required before hot-melt coating.

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Nomenclature

API	Active pharmaceutical ingredient
CA	Coating amount ($\%_{w/w}$)
c_s	Screw constant (kg)
D	Roller diameter (m)
DoE	Design of experiments
DSC	Differential scanning calorimetry
γ_R	Ribbon relative density (−)
GPM	α-D-glucopyranosyl-1-6-mannitol
GPS	α-D-glucopyranosyl-1-6-sorbitol
HLB	Hydrophilic lipophilic balance
HMC	Hot-melt coating
HPLC	High performance liquid chromatography
m	Mass throughput (kg/s)
MCC	Microcrystalline cellulose
N_R	Roller speed (s^{-1})
N_S	Screw speed (s^{-1})
O/W	Oil in water
ρ	True density (kg/m^3)
PDA	Photodiode array
PET	Polyethylene terephthalate
PSD	Particle size distribution
PVP	Polyvinylpyrrolidone
S	Roller gap (m)
SEM	Scanning electron microscopy
SWAXS	Small and wide angle X-ray scattering
W	Roller width (m)

In the pharmaceutical industry, using dry granulation via roller compaction and/or slugging dates back to the late 1940s (Miller, 2005). However, in the 21st century roller compaction has attracted renewed scientific attention, especially due to the transition of equipment from manual to automatic that resulted in a higher level of process control (Guigon et al., 2007; Khorasani et al., 2016; Miller, 2005; Osborne et al., 2013). Similarly to hot-melt coating, roller compaction is a solvent-free technology resulting in a fast and cost-effective manufacturing process, since time-consuming evaporation steps or costly solvent recovery and disposal are not required (Guigon et al., 2007; Jannin and Cuppok, 2013; Jozwiakowski et al., 1990; Miller, 2005). Furthermore, during roller compaction, the density of ribbon and granules can be increased by applying higher pressures (Hancock et al., 2003; Teng et al., 2009). These densified granules are suitable for hot-melt coating purposes. Additionally, it is critical that the resulting granules are resistant to the mechanical stress involved in the fluid bed hot-melt coating process since air velocity may result in pulverization of fragile granules (Jozwiakowski et al., 1990).

During a roller compaction process, powder friction at the surface of the rollers first increases the pressure exerted to the powder. Next, this compression pressure alone is responsible for the bonding of particles in different stages: (1) particle rearrangement; (2) particle deformation; (3) particle fragmentation; and (4) particle bonding (Miller, 2005; Mollet and Grubenmann, 2001; Yu et al., 2012). Applying roller compaction technology to producing granules with a high content of ibuprofen sodium is known to be challenging (Gruber and Reher, 2004). The reasons are the extremely poor compactibility of ibuprofen sodium powder and the low frictional properties (internal and wall friction) that are not suitable for granule formation via roller compaction (Higton, 1999; Gruber and Reher, 2004).

The aim of this work is to produce granules with high ibuprofen sodium content, dense and abrasion-resistant via roller compaction and investigate their resulting solid state. A second goal is to evaluate the effect of hot-melt coating parameters on taste-masking and *in vitro* immediate release profile of obtained ibuprofen sodium granules using a statistical design of experiments (DoE).

2. Material and methods

2.1. Material

Ibuprofen sodium dihydrate was purchased from BASF (Ludwigshafen, Germany). The roller compaction excipients sorbitol (Parteck® SI 150) and mannitol (Parteck® M200) were purchased from Merck (Darmstadt, Germany). Isomalt (galenIQ™ 721) was purchased from Beneo (Mannheim, Germany). Polyvinylpyrrolidone (PVP) (Kollidon® 25) was obtained from BASF (Ludwigshafen, Germany), and microcrystalline cellulose (Avicel® pH 105) was purchased from FMC (Philadelphia, PA USA). The coating material tripalmitin (Dynasan®116) was generously provided by IOI Oleo GmbH (Witten, Germany) and polysorbate 65 (Tween®65) was obtained from Croda GmbH (Nettetal Kaldenkirchen, Germany). All other chemicals were of analytical grade and purchased from Sigma-Aldrich (Steinheim, Germany).

2.2. Methods

2.2.1. Manufacturing of ibuprofen sodium granules

Table 1 lists the formulations selected for roller compaction excipient screening, throughput evaluation and process robustness. Raw material was de-agglomerated by sieving before further processing (sieve screen 1 mm). Blends for excipient screening trials (600 g) were prepared using a Stephan mixer (Stephan

Table 1
List of roller compaction formulations employed.

Ibuprofen Sodium ($\%_{w/w}$)	Microcrystalline cellulose($\%_{w/w}$)	PVP K25 ($\%_{w/w}$)	Mannitol ($\%_{w/w}$)	Isomalt ($\%_{w/w}$)	Sorbitol ($\%_{w/w}$)
Excipient screening					
95; 90; 80;70	5; 10; 20; 30	–	–	–	–
90; 80; 70	–	10; 20; 30	–	–	–
95;90;80	–	–	5; 10; 20	–	–
95;90	–	–	–	5; 10	–
98; 95;92	–	–	–	–	2; 5; 8
Throughput evaluation					
94	–	–	–	3.5	2.5
Process robustness					
94	–	–	–	3.5	2.5

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