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Advanced stable lipid-based formulations for a patient-centric product design

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ABSTRACT

Multiparticulate dosage forms are a recent strategy to meet the special needs of children, elderly people and patients suffering from dysphagia. Our study presents a novel and cost-efficient approach for the manufacturing of a taste-masked multiparticulate system with a stable immediate release profile by applying lipid-based excipients in a solvent-free hot melt coating process.

The thermosensitive *N*-acetylcysteine (*N*-ac) was used as model drug and hot-melt coated with a mixture of tripalmitin and polysorbate 65.

A predictive *in vitro* method for the evaluation of the taste masking efficiency was developed based on the deprotonation of the carboxyl group of *N*-ac and the decline of pH, responsible for the unpleasant sour taste of the compound. The method was confirmed using *in vivo* studies. Differential scanning calorimetry and X-ray scattering experiments revealed polymorphic transformation and its dependency on transformation time, temperature and emulsifier concentration. During the process, the coating was transformed almost completely into the stable β-polymorph, leading to an unaltered dissolution profile during storage. A statistical design was conducted that revealed the critical process parameters affecting the taste masking efficiency and drug release.

This study shows the successful application of solvent-free hot-melt coating in the development of a taste-masked and stable formulation.

1. Introduction

According to the World Health Organization (WHO) patient adherence, defined by the extent to which patients follow an envisaged therapeutic regime, severely effects the health system efficiency and the therapeutic outcome (Sabaté, 2003). An efficient strategy to enhance this adherence is a population driven, patient centric design of dosage forms that considers the intended product performance and patient needs (FitzPatrick, 2014). Multiparticulate drug delivery systems such as “direct to mouth” granules appear to meet these requirements. The application of discrete small particles instead of a monolithic unit offers numerous advantages such as an enhanced bioavailability because of a greater surface area, a reduced risk of dose dumping or peak-to-trough plasma fluctuations in case of controlled release formulations and facilitation of the swallowability for patients of the geriatric or pediatric population, suffering from dysphagia (Gandhi and Baheti, 2013; Patel and Dhake, 2011; Patwekar and Baramade, 2012; Sharma and Chaurasia, 2013). Nevertheless, successful taste masking of drugs with an unpleasant taste is a common obstacle. Discrete particle coating in a fluid bed coater seemed to be an appropriate approach for this demand (Alkire et al., 1997; Douroumis, 2007; Kolhe et al., 2009). In particular, hot-melt fluid

Abbreviations: AIR, airflow; API, active pharmaceutical ingredient; CA, coating amount; DOE, design of experiment; DSC, differential scanning calorimetry/calorimeter; EMU, emulsifier content; GRAS, generally recognized as safe; HLB, hydrophilic lipophilic balance; HPLC, high performance liquid chromatography; IR, infrared; MCE, mixed cellulose ester; *N*-ac, *N*-acetylcysteine; PSD, particle size distribution; R2, model fit; SEM, scanning electron microscopy; SP, spray pressure; SR, spray rate; Q2, future prediction precision; WAXS, wide-angle X-ray scattering; WHO, world health organization.

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bed spray coating provides numerous outstanding advantages due to the avoidance of organic and aqueous solvents. This results in a faster and more cost-effective manufacturing process, since time-consuming evaporation steps or costly solvent recovery and disposal are not required. Additionally, the most frequently applied excipients originate from lipids, which exist in nature, are comparatively cheap and "generally recognized as safe" (GRAS) (Jannin and Cuppok, 2013). Their excellent slippage properties cause a smooth and pleasant mouth feeling, which can be appreciated by patients suffering from dysphagia. However, a few challenges are raised by the application of lipid-based excipients. Depending on their chemical structure, these materials are capable to form several crystalline structures with different thermodynamic stabilities and physicochemical properties. Transformation into a thermodynamically more stable structure may result in the alteration of the dissolution properties and of both microscopic and macroscopic structural morphology (known as "blooming"), influencing the long-term stability of these formulations (Khan and Craig, 2004). Another issue is the hydrophobic nature of these excipients, if immediate release is the aim. Although this property results in near savorlessness, making these substances excellent coating excipients for taste masking of drugs, the dissolution rate is often retarded. The objective of this work is the development of a taste-masked multiparticulate system with an unaltered immediate drug release profile during storage by using hot-melt spray coating with lipid excipients in a fluid bed coater. The thermosensitive *N*-ac, exhibiting an unpleasant sour taste, was selected as the model drug for this study.

2. Material and methods

2.1. Material

The active pharmaceutical ingredient (API) *N*-ac was purchased from PharmaZell GmbH (Raubling, Germany). The coating material tripalmitin (Dynasan® 116) was kindly provided by Cremer Oleo Division (Witten, Germany) and polysorbate 65 (Tween® 65) and Brij® 30 were obtained from Croda GmbH (Nettetal Kaldenkirchen, Germany). Hydrochloric acid 37%, HPLC grade acetonitrile and phosphoric acid 85% were purchased from Sigma–Aldrich (Steinheim, Germany) and Sorbitol Parteck Si 150 from Merck KGaA (Darmstadt, Germany).

2.2. Methods

2.2.1. Manufacturing method for particle coating (fluid bed hot-melt spray coating)

Fluid bed hot-melt spray coating was chosen as the manufacturing method for coating particles in order to produce drug-loaded microcapsules. In this process, the feed material is maintained in a fluidized state in the fluid bed container. The molten coating material is sprayed onto the fluidized particles and resolidifies on their surface, thereby forming a coating layer (Becker et al., 2013). In this study, the fluid bed hot melt coating was performed using an Innojet® Ventilus® V-2.5 laboratory system fluid bed device with an IHD-1 hot melt device (Romaco Innojet GmbH, Steinen, Germany) using a 3 L metal container. The manufacturing took place at two different laboratories located at separate sites. Only the machine in one laboratory was equipped with an additional cooling and dehumidification device but that site lacked an opportunity to execute differential scanning calorimetry (DSC) and wide-angle X-ray scattering (WAXS) measurements. The room in which the machine without a cooling device was used had an average temperature of 24 °C ± 1 °C and a relative humidity of 47% r.h. ± 6% r.h. The inlet temperature was set to room temperature (24 °C ± 1 °C) and, 20 °C, for the machines without and with cooling device, respectively, to prevent degradation of *N*-ac (Stanislaus and Klemm, 1992) and to reduce the agglomeration tendency (Becker et al., 2013). The temperature of the melt and the spray air were set to 100 °C. The product temperature was continuously recorded with an IR-sensor and lay 9 °C ± 2 °C above the adjusted inlet air temperature depending on the parameter setting. A batch size of 800 g was used for all experiments to ensure optimal loading of the fluid bed container and to obtain a homogenous fluidization during the entire coating process. MODDE 10 (Umetrics, Sweden) was used as the software for creating a statistical model in order to analyze the output parameters of the hot melt coating process. A Rechtschaffner quadratic model with 24 runs was chosen to evaluate the main and two-factor interactions of the input parameters spray rate, spray pressure, coating amount, emulsifier content and air flow rate on the output parameters dissolution rate, taste masking efficiency and PSD (Qu, 2007). A multiple linear regression analysis was applied for the fitting and modeling of the data. Table 1 shows the input parameter settings used for building the statistical model. These settings were selected based on extensive preliminary studies. The spray rate was determined using an electronic connection of the fluid bed coater with a balance weighing the loss of the melt container.

Table 2 demonstrates the design of experiments created with the software. The input parameter settings for the 24 runs and the related results of the output parameters are listed in this table. The data obtained from dissolution testing (time needed for 85% release of API from coated particles), the pH-measurements as an indicator for the taste masking efficiency and PSD (x_{90}/x_{10}) were evaluated as output parameters.

2.2.2. Analytical methods

2.2.2.1. Dissolution profile of the hot-melt coated N-ac particles. The dissolution tests were performed in an USP 2 offline system (Erweka, Heusenstamm, Germany) apparatus. The conditions are listed in Table 3. At each sampling point, 1 mL of the dissolution medium was taken by hand using a syringe and filtered (MCE membrane, diameter 13 mm, pore size 0.22 μm; Merz Brothers GmbH, Haid, Austria) into HPLC-vials. The removed medium was not substituted but considered in the following calculations.

The content assay was performed with a sample mass of the coated particles comprising approximately 50 mg of *N*-ac. The sample was weighed into a 100 mL volumetric flask and 50 mL of 0.1 N hydrochloric acid were added by using a volumetric pipette. After tightly closing the volumetric flask, the samples were treated in an ultrasonic bath for 15 min while shaking every third minute

Table 1
Input parameter settings for the Rechtschaffner DOE.

Input parameters	−1	0	+1
Spray rate [g/min]	4	7	10
Spray pressure [bar]	0.50	0.65	0.80
Percentage of the coating material in the coated *N*-ac particles [%]	25.0	32.5	40.0
Percentage of polysorbate 65 in the coating material [%]	10	20	30
Air flow rate [m^3/h]	45	53	60