International Journal of Pharmaceutics 517 (2017) 403–412

Contents lists available at ScienceDirect

International Journal of Pharmaceutics

journal homepage: www.elsevier.com/locate/ijpharm

Microphase separation in solid lipid dosage forms as the cause of drug release instability

Diogo Gomes Lopes[a,b], Ioannis Koutsamanis[a,b], Karin Becker[b], Otto Scheibelhofer[a], Peter Laggner[a,c], Detlev Haack[d], Michael Stehr[e], Andreas Zimmer[b], Sharareh Salar-Behzadi[a,*]

[a] Research Center Pharmaceutical Engineering GmbH, Graz, Austria
[b] Institute of Pharmaceutical Science, Department of Pharmaceutical Technology, University of Graz, Austria
[c] Bruker AXS GmbH, Graz, Austria
[d] Hermes Arzneimittel GmbH, Großhesselohe, Germany
[e] IOI Oleo GmbH, Witten, Germany

ARTICLE INFO

Article history:
Received 9 September 2016
Received in revised form 6 December 2016
Accepted 17 December 2016
Available online 19 December 2016

Keywords:
Solid lipid excipients
Drug release stability
Hot-melt coating
Polymorphism
Microphase separation

ABSTRACT

Although lipid excipients are of increasing interest for development of taste-masked and modified release formulations, the drug release instability and the lack of mechanistic understanding in that regard still prevent their larger-scale application. In this work, we investigated the physical stability of a binary (tripalmitin/polysorbate 65) lipid coating formulation with a known stable polymorphism. The coating composition was characterized using DSC to construct the phase diagram of binary system and polarized light microscopy to display the microstructure organization. The water uptake and the erosion of slabs cast from the coating formulations were investigated post-production and after storage. Subsequently, *N*-acetylcysteine particles were coated with the selected formulations and the drug release stability was investigated. Additionally, microstructure characterization was performed *via* SEM and X-ray diffraction. The drug release instability was explained by polysorbate 65 and tripalmitin phase growth during storage, especially at 40 °C, suggesting that polysorbate 65 can leak out of tripalmitin spherulitic structures, creating lipophilic and impermeable tripalmitin regions. The growth of polysorbate 65 phase leads to larger hydrophilic channels with reduced tortuosity. This work indicates that for obtaining stable drug release profiles from advanced lipid formulations, microphase separation should be prevented during storage.

1. Introduction

Pharmaceutical scientists are increasingly using lipid-based excipients in the development of solid oral dosage forms for taste masking (Lopes et al., 2016; Becker et al., 2016; Eckert et al., 2014) and as sustained release agents (Jannin and Cuppok, 2013; Jeong et al., 2015; Jannin et al., 2015). The interest in this class of excipients is growing mainly since they can be applied in a variety of processes and since they are naturally occurring compounds that are predominantly digestible and Generally Recognized as Safe (GRAS) (Jannin and Cuppok, 2013). Due to these characteristics, lipid-based excipients can be used to generate new intellectual property by reformulating the existing dosage forms. However, they are known to cause instability of final products, and a good understanding and monitoring of the solid state behavior is required to obtain reliable and reproducible dosage forms (Jannin et al., 2015; Becker et al., 2015; Khan and Craig, 2004; Witzleb et al., 2012; Chansaroj et al., 2007; Qi et al., 2010; Reitz and Kleinebudde, 2007a,b; Oliveira et al., 2013; Aleksovski et al., 2016; Vervaeck et al., 2013; Kreye et al., 2011).

A complex solid state of such dosage forms results from the structural hierarchy of the lipid-based excipients. Often, this complexity originates from the excipient's composition, in which triacylglycerols (TAGs) are combined with diacylglycerols, monoacylgylcerols, free fatty acids, phospholipids or surfactants (Lopes et al., 2016; Becker et al., 2016, 2015; Jannin and Cuppok, 2013; Rosiaux et al., 2014; Windbergs et al., 2009). TAGs can crystallize

* Corresponding author at: Research Center Pharmaceutical Engineering GmbH, Inffeldgasse 13, 8010 Graz, Austria.
E-mail address: sharareh.salar-behzadi@rcpe.at (S. Salar-Behzadi).

http://dx.doi.org/10.1016/j.ijpharm.2016.12.040
0378-5173/

into different crystal structures, giving rise to monotropic polymorphism (Chapman, 1962). On the nano- and meso-scales, the TAG crystallites are lamellar structures with an estimated thickness of 20–80 nm and lateral distances of 100–1000 nm (Peyronel et al., 2015; Acevedo and Marangoni 2010; Marangoni and Pink, 2012). The crystallites are arranged into spherulitic structures (Ueno et al., 2008), creating a polycrystalline matrix in which the minor components are trapped within nanospaces (Peyronel et al., 2015).

Several studies on the instability of drug release have described TAG polymorphism during storage (Jannin et al., 2015; Witzleb et al., 2012; Chansaroj et al., 2007; Vervaeck et al., 2013), indicating that drug release can be unstable despite the stable molecular packing (Jannin et al., 2015; Khan and Craig, 2004; Kreye et al., 2011). This suggests that solid state changes occur at the supra-molecular level during storage. A better understanding of the underlying instability mechanisms is essential for developing stable lipid formulations.

In this work, we examined the instability of a binary system composed of TAG tripalmitin and surfactant polysorbate 65. In a recent study, it was shown that polysorbate 65 ($\geq 10\%_{w/w}$) accelerates the polymorphic transformation of tripalmitin into the stable β-form during a fluid bed hot-melt spray coating process (Becker et al., 2016). The final dosage form is a taste-masked multiparticulate system with a stable immediate release profile and a stable polymorphism (Becker et al., 2016). However, at higher coating levels and slower drug release rates, we observed the drug release instability. In the current work, in order to understand the instability mechanisms, we characterized the binary system *via* a phase diagram, 2-D polarized light micrographs and water uptake and erosion studies. Subsequently, the coating formulations were used to manufacture hot-melt coated particles of *N*-acetylcysteine, and the drug release stability during storage was evaluated. In addition, the characterizations of microstructure and nanoscale were performed *via* scanning electron microscopy and small angle X-ray scattering, respectively.

2. Material and methods

2.1. Material

The active pharmaceutical ingredient (API) *N*-acetylcysteine was purchased from PharmaZell GmbH (Raubling, Germany). The coating material tripalmitin (Dynasan® 116) was kindly provided by IOI Oleo GmbH (Witten, Germany), and polysorbate 65 (Tween® 65) was obtained from Croda GmbH (Nettetal Kaldenkirchen, Germany). Hydrochloric acid 37%, HPLC grade acetonitrile and phosphoric acid 85% were purchased from Sigma–Aldrich (Steinheim, Germany).

2.2. Methods

2.2.1. Characterization of coating formulation

2.2.1.1. Construction of phase diagram. Modulated differential scanning calorimetry (204 F1 Phoenix Netzsch GmbH, Selb, Germany) was applied to construct the phase diagram. Nitrogen was used as a protective and purge gas (flow-rate of 50 ml/min). Physical mixtures were prepared as polysorbate 65 concentrations of 10, 25, 50, 75, and $90\%_{w/w}$ in tripalmitin. The samples were melted at 90 °C and stirred with a magnetic stirrer for at least 5 min before weighing 2–3 mg into aluminum pans and sealing them with pierced lids. The samples were stored for 4 weeks at 20 °C to give the system thermodynamic stability. For modulated differential scanning calorimetry analysis, the samples were balanced at −20 °C for 5 min and heated to 90 °C at an average heating rate of 2 K/min with an amplitude of 0.21 K and a period of 40 s. Pure tripalmitin and polysorbate 65 were analyzed using the same program. All measurements were performed in triplicate. The melting endotherm onset was considered as the phase melting point and used to construct the phase diagram.

2.2.1.2. Microstructure analysis of coating formulations. The microstructure of coating formulations, containing $10\%_{w/w}$ and $30\%_{w/w}$ polysorbate 65 in tripalmitin was characterized by 2-D polarized light microscopy. The physical mixtures were melted at 90 °C and stirred with a magnetic stirrer for at least 5 min before a drop (about 10 μL) of the molten formulation was placed on a heated cover slip (90 °C) and covered with another heated cover slip (90 °C). Next, the sample was placed into a hot stage unit (Linkam THMS 600, Tadworth, UK) coupled to a polarized light microscope (Olympus BX51M, PA, USA).

In order to simulate crystallization during the hot-melt coating process, the sample was treated as proposed in the DSC studies by Becker et al. (2016). This publication described a complete transformation of the α-form into the stable β-form of tripalmitin within less than 10 min, using at least 10% of polysorbate 65 at 35 °C. In the current study, the sample was heated to 90 °C and equilibrated at this temperature for 5 min. Next, the sample was cooled to 35 °C at 10 K/min and kept at this temperature for 10 min in order to promote a complete transformation from the α-form into the stable β-form of tripalmitin. To simulate the completion of coating process, the sample was subsequently cooled to 20 °C at 10 K/min and micrographs were taken.

2.2.1.3. Water uptake and erosion of coating formulations. The rate and extent of water uptake and the erosion of slabs cast from the coating formulations were evaluated. Concentrations of polysorbate 65 of $10\%_{w/w}$ and $30\%_{w/w}$ in tripalmitin were selected. The physical mixtures were melted at 90 °C and stirred with a magnetic stirrer for at least 5 min. Next, the melted formulations were poured into pre-heated (90 °C) silicone molds (40 mm long, 10 mm wide and 2 mm thick). The samples were cooled down to room temperature (20 °C). The slab surfaces were trimmed with a scalpel in order to achieve a final thickness of about 2 mm.

Each slab (about 750 mg) was carefully weighed [dry mass (0)] and placed into a glass vial containing 15 mL of pre-heated (37 °C) ultra-purified water (Milli-Q, Merck Life Science, Darmstadt, Germany). After 10, 15 and 20 days, the slabs were withdrawn, the excess surface water was carefully removed, and the systems were accurately weighed [wet mass (t)] (g) and dried to achieve a constant weight in a drying oven at 40 °C (dry mass t) (g). The water content (%) (t) and the slab erosion (%) (t) were calculated as follows:

$$\text{Water content (\%) (t)} = [\text{wet mass (t)} - \text{dry mass (t)}]/\text{wet mass (t)} \times 100\% \quad (1)$$

$$\text{Slab erosion (\%) (t)} = [\text{dry mass (0)} - \text{dry mass (t)}]/\text{dry mass (0)} \times 100\% \quad (2)$$

where dry mass (0) (g) denotes the dry mass of the slab at t = 0.

The trials were undertaken in triplicates. The investigations of water uptake and sample erosion were conducted for slabs after the preparation and after one month of storage at 20 °C and 40 °C. The samples were balanced at 20 °C for 24 h prior to the water uptake and erosion studies.