International Journal of Pharmaceutics 499 (2016) 90–100

Contents lists available at ScienceDirect

International Journal of Pharmaceutics

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

Molecularly designed lipid microdomains for solid dispersions using a polymer/inorganic carrier matrix produced by hot-melt extrusion

Camille Adler[a,b], Monica Schönenberger[c], Alexandra Teleki[d], Martin Kuentz[a,*]

[a] University of Applied Sciences and Arts Northwestern Switzerland, Institute of Pharmaceutical Technology, Gründenstrasse 40, 4132 Muttenz, Switzerland
[b] University of Basel, Institute of Pharmaceutical Technology, Klingelbergstrasse 50, 4056 Basel, Switzerland
[c] Swiss Nanoscience Institute, Nanotech Service Lab, Klingelbergstrasse 82, 4056 Basel, Switzerland
[d] DSM Nutritional Products Ltd., R&D Center Formulation & Application, P.O. Box 2676, 4002 Basel, Switzerland

ARTICLE INFO

Article history:
Received 23 November 2015
Received in revised form 18 December 2015
Accepted 19 December 2015
Available online 22 December 2015

Keywords:
Hot-melt extrusion
Acidic lipid
Inorganic carrier
Designed lipid microdomains
Interactions

ABSTRACT

Amorphous solid dispersions have for many years been a focus in oral formulations, especially in combination with a hot-melt extrusion process. The present work targets a novel approach with a system based on a fatty acid, a polymer and an inorganic carrier. It was intended to adsorb the acidic lipid by specific molecular interactions onto the solid carrier to design disorder in the alkyl chains of the lipid. Such designed lipid microdomains (DLM) were created as a new microstructure to accommodate a compound in a solid dispersion. Vibrational spectroscopy, X-ray powder diffraction, atomic force microscopy as well as electron microscopic imaging were employed to study a system of stearic acid, hydroxypropylcellulose and aluminum magnesium silicate. β-carotene was used as a poorly water-soluble model substance that is difficult to formulate with conventional solid dispersion formulations. The results indicated that the targeted molecular excipient interactions indeed led to DLMs for specific compositions. The different methods provided complementary aspects and important insights into the created microstructure. The novel delivery system appeared to be especially promising for the formulation of oral compounds that exhibit both high crystal energy and lipophilicity.

1. Introduction

Solid dispersions (SDs) represent one of the most successful strategies to improve the solubility and bioavailability of poorly water-soluble compounds (Janssens and Van den Mooter, 2009). The first generation of SDs comprised crystalline carriers (e.g., urea or mannitol) and was developed in the 1960s. The second generation of SDs emerged in the 1970s with the replacement of crystalline excipients by amorphous matrices (e.g., polymers or sugar glasses) to overcome the low release rate of crystalline SDs. However, the supersaturated state of the compound in the polymeric carrier led to its precipitation and crystallization, which negatively affected the release rate and drug absorption (Vasconcelos et al., 2007; Vo et al., 2013). Another problem of several formulations was their rather poor dispersibility in aqueous media such as gastrointestinal fluids, and therefore a third generation of SDs was developed in the 1980s. Serajuddin proposed that the use of surface active agents (e.g., lipid excipients) as carriers or in combination with polymers can be beneficial in several formulations with respect to anhydrous SDs and was deemed as particularly advantageous for the dispersion behavior in aqueous media (Serajuddin, 1999).

Among the different SD preparation techniques such as spray drying, solvent evaporation or melt agglomeration methods, hot-melt extrusion (HME) has become a common manufacturing process over the last two decades (Vo et al., 2013). HME has several advantages such as being a solvent free and continuous process with high applicability and scalability (Repka et al., 2012). The most commonly used matrices are thermoplastic polymers like cellulose derivatives, polyethylene oxides, or polyvinyl pyrrolidone (Repka et al., 2013). In addition to polymers, other excipients can also be used as carriers for HME, and a few reports showed that, as with the melt-adsorption method, stable melt-extruded amorphous SDs could be produced by adsorbing an active compound onto an inorganic carrier (Maclean et al., 2011; Sruti et al., 2013). There are hence different ways to molecularly disperse a compound in a matrix or to convert it into small amorphous domains.

To explore the full potential of amorphous systems, the development of new microstructures would be of high interest. The aim of this study was within this scope to target designed lipid microdomains (DLMs) for delivery systems by HME. This new

---

[*] Corresponding author. Fax: +41 61 467 47 01.
E-mail address: martin.kuentz@fhnw.ch (M. Kuentz).

http://dx.doi.org/10.1016/j.ijpharm.2015.12.057
0378-5173/© 2015 Elsevier B.V. All rights reserved.

approach is based on a combination of a lipid, a polymer and an adsorbent. The lipid was here meant to adsorb onto the carrier surface to obtain disordered microdomains of lipid alkyl chains to accommodate an active compound. In contrast, previous studies by Gupta et al. (2003) and Maclean et al. (2011) intended the amorphization of an acidic drug by direct adsorption onto an inorganic carrier like aluminum magnesium silicate (AMS). They showed that the acidic moiety of the compounds interacted with silicate silanol groups through H-bonds and with magnesium and aluminum ions present on the adsorbent surface through ion-dipole interactions. These interactions drove the amorphization and stabilization of the acidic drugs. Our novel approach was to employ a fatty acid to adsorb onto the AMS inorganic carrier to achieve the aforementioned DLMs for amorphous drug delivery.

The DLM formulations were prepared by HME. Hydroxypropylcellulose (HPC) was used as an immediate or controlled release polymer, and stearic acid (SA) was employed as plasticizer and acidic lipid to interact with AMS (Neusilin US2). The first aim was a proof-of-concept regarding the technical feasibility of DLM formulations. The influence of AMS on SA crystallinity was studied in the melt extrudates by X-ray powder diffraction (XRPD), atomic force microscopy (AFM), and scanning electron microscopy (SEM). Interactions between the lipid and the inert material were investigated by attenuated total reflectance Fourier-transform infrared (ATR-FTIR) spectroscopy. The second aim was then to use the DLM delivery system to formulate a model compound, i.e., β-carotene (BC).

2. Materials and methods

2.1. Materials

HPC (Klucel EF Pharm) was kindly donated by Ashland (Schaffhausen, Switzerland). *N*-hexane (purity ≥99%), dichloromethane (purity ≥99.5%), cyclohexane (purity 99.5%), methanol (purity 99.8%), ethanol (purity ≥ 99.5%), and acetonitrile (purity ≥99.9%) were obtained from Merck (Darmstadt, Germany). Butylated hydroxytoluene (purity ≥99%), tetrahydrofuran (purity ≥99.5%), *N*-ethyldiisopropylamine (purity ≥98%), 2-propanol (purity ≥98%), ammonium acetate (purity ≥98%) and stearic acid were purchased from Sigma–Aldrich (Steinheim, Germany). AMS (Neusilin US2) was obtained from Fuji Chemical Industry Co., Ltd. (Toyama, Japan). Crystalline β-carotene (BC) was supplied by DSM Nutritional Products Ltd. (Basel, Switzerland).

2.2. Hot-melt extrusion

HPC, SA and AMS were weighed and premixed with a spatula at different ratios. Table 1 summarizes the different compositions of the extrudates that were prepared by the HME process using a Thermo Scientific Haake MiniLab II conical, co-rotating, twin-screw microcompounder (Thermo Electron, Karlsruhe, Germany). The premix was manually fed into the extruder hopper and the temperature of the barrel was set to 160 °C. The screw speed during the feeding step was 50 rpm, followed by one minute mixing at 250 rpm. Subsequently, the extrudate strand was allowed to exit from the flat die by opening the bypass valve. The strands were stored in the fridge until analysis. Extrusion with BC (3%, w/w) was performed using the same conditions. The BC strands were stored in sealed aluminum bags purged with nitrogen until analysis. The placebo samples and BC formulations will be denoted HPC/SA/AMS and HPC/SA/AMS/BC, respectively. The most promising formulation containing 70/10/20% (w/w) HPC/SA/AMS, will be named designed lipid microdomain (DLM) system.

Table 1
Formulation composition of extrudate strands produced by HME.

HPC (%, w/w)	SA (%, w/w)	AMS (%, w/w)	BC (%,w/w)
100	0	0	0
90	10	0	0
85	10	5	0
80	10	10	0
75	10	15	0
70	10	20	0[a]
80	0	20	0
97	0	0	3
87	10	0	3
77	0	20	3
67	10	20	3[b]

HME = hot-melt extrusion; HPC = hydroxypropylcellulose; SA = stearicacid; AMS = aluminum magnesium silicate; BC = β-carotene.

[a] Designed lipid microdomain (DLM) formulation.

[b] DLM formulation containing 3% (w/w) BC.

2.3. Time-domain nuclear magnetic resonance

The solid fat content (SFC) of raw SA was measured by time-domain NMR (TD-NMR) using a minispec mq 20 (Bruker BioSpin GmbH, Rheinstetten, Germany). Since the samples were analyzed with an indirect method, olive oil was used as a reference. The lipid powder and the olive oil were filled into separate 18 mm diameter test tubes (20 mm filling height) and heated at 100 °C in an oven for 45 min. A serial tempering method was used for the SFC analysis. The tubes were placed at 0 °C (ice-bath) for 60 min before the first measurement. The subsequent measurements were carried out over a range of 10–80 °C, following an equilibration time of 30 min at each temperature. For each tube, the samples were scanned four times with a frequency of 19.95 MHz and a pulse attenuation of 11 dB. The SFC was calculated from Eq. (1) (Marangoni and Wesdorp, 2012):

$$\mathrm{SFC}(\%) = 100 - \frac{\mathrm{Sample}^{80^\circ\mathrm{C}} \times \mathrm{Oil}^{T}}{\mathrm{Sample}^{T} \times \mathrm{Oil}^{80^\circ\mathrm{C}}} \times 100 \tag{1}$$

where Sample and Oil correspond to the signal intensities obtained for the sample and the olive oil, respectively. *T* is the temperature at which the measurement was carried out, and 80 °C is the final measurement temperature.

2.4. X-ray powder diffraction

XRPD patterns were obtained using a D2 Phaser diffractometer (Bruker AXS GmbH, Karlsruhe, Germany) configured with a fast linear 1-D Lynxeye detector. The radiation was provided by a 1.8 kW Co KFL tube (wavelength = 1.79 Å) working with a Fe filter. The applied voltage and current were 30 kV and 10 mA, respectively. Instead of being milled, the extrudate strands were cut into 2–2.5 cm long pieces to avoid the potential recrystallization of the lipid. Four of these pieces were positioned in parallel in a sample holder and analyzed at room temperature over the 2θ range of 6–37°. The time per step was 3 s, and the increment was 0.02° (2θ). SA crystallite size was estimated using the Diffrac.Eva v 4.0 software (Bruker AXS GmbH, Karlsruhe, Germany). Sizes were evaluated by means of Scherrer equation from the full width at half maximum of selected peaks.

2.5. Attenuated total reflectance Fourier-transform infrared spectroscopy

ATR-FTIR spectra of pure compounds and extrudates were acquired in the 4000–600 cm^{-1} range using a Varian 670 IR spectrometer (Varian Inc., Palo Alto, CA, USA) equipped with a golden gate high temperature heated diamond ATR top plate