European Journal of Pharmaceutics and Biopharmaceutics 92 (2015) 83–95

Contents lists available at ScienceDirect

European Journal of Pharmaceutics and Biopharmaceutics

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

Research Paper

Alcohol dose dumping: The influence of ethanol on hot-melt extruded pellets comprising solid lipids

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ARTICLE INFO

Article history:
Received 8 August 2014
Revised 18 February 2015
Accepted in revised form 22 February 2015
Available online 28 February 2015

Keywords:
Alcohol dose dumping
Solid lipids
Calcium stearate
Controlled-release
Hot-melt extrusion

ABSTRACT

The objective of the present study was to investigate interactions between alcohol and hot-melt extruded pellets and the resulting drug release behavior. The pellets were composed of vegetable calcium stearate as matrix carrier and paracetamol or codeine phosphate as model drugs. Two solid lipids (Compritol® and Precirol®) were incorporated into the matrix to form robust/compact pellets. The drug release characteristics were a strong function of the API solubility, the addition of solid lipids, the dissolution media composition (i.e., alcohol concentration) and correspondingly, the pellet wettability. Pellets comprising paracetamol, which is highly soluble in ethanol, showed alcohol dose dumping regardless of the matrix composition. The wettability increased with increasing ethanol concentrations due to higher paracetamol solubilities yielding increased dissolution rates. For pellets containing codeine phosphate, which has a lower solubility in ethanol than in acidic media, the wettability was a function of the matrix composition. Dose dumping occurred for formulations comprising solid lipids as they showed increased wettabilities with increasing ethanol concentrations. In contrast, pellets comprising calcium stearate as single matrix component showed robustness in alcoholic media due to wettabilities that were not affected by the addition of ethanol.

The results clearly indicate that the physico-chemical properties of the drug and the matrix systems are crucial for the design of ethanol-resistant dosage forms. Moreover, hydrophobic calcium stearate can be considered a suitable matrix system that minimizes the risk of ethanol-induced dose dumping for certain API's.

1. Introduction

Alcohol-induced dose dumping of controlled-release oral dosage forms containing opioid and non-opioid drugs with narrow therapeutic ranges is a significant challenge in the formulation development. Since alcohol may alter the release-rate-controlling mechanism of the formulation, possibly resulting in an immediate and uncontrolled drug release, the concomitant intake of alcoholic beverages together with such dosage forms poses a serious safety concern. This phenomenon, known as alcohol-induced dose dumping (ADD), can have dangerous effects [1]. Particularly susceptible are controlled-release formulations that contain a high total amount of API in order to reduce the dosing frequency and prolong the therapeutic effect. In 2005, Palladone™, a hydromorphone modified-release capsule formulation, was withdrawn from the US market, since taking it together with alcohol drastically increased the peak plasma concentrations of hydromorphone by causing failure in the release-rate-controlling mechanism [2]. Such opioid-overdose may lead to respiratory depression followed by hypoxia and even death [3]. To test for possible alcohol dose dumping effects, the Food and Drug Administration (FDA) recommends to conduct *in vitro* drug release studies in ethanolic media of controlled-release dosage forms containing opioid and non-opioid drugs with a narrow therapeutic range [1,4].

To date, only a limited number of robust single unit dosage forms [5], such as osmotic drug delivery devices [6,7] and controlled-release matrix systems [8–15] that can withstand the effect of alcohol, are available. For the former one, a controlled-release tablet formulation of oral hydromorphone was developed using a patented oral osmotic (OROS®) Push–Pull delivery system [6]. It was shown that the controlled-release properties remained unchanged in the

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http://dx.doi.org/10.1016/j.ejpb.2015.02.022
0939-6411/

presence of alcohol and no dose dumping of hydromorphone occurred [6]. The same effect was reported by Koziara et al. [7]: although increasing ethanol concentrations up to 60% caused a slight increase in the drug release of OROS® systems, controlled-release properties of the drug delivery system remained unaffected and no dose dumping occurred. This could be attributed to the specific OROS® technology, which is designed such that the drug release rate is actively controlled by the dosage form, regardless of such environmental factors as gastrointestinal motility, surrounding pH and presence of food and alcohol [16]. In the field of matrix systems and alcohol-robust controlled-release matrix tablets, hydrophilic polymers (e.g., polyethylene oxide [8], cross-linked high amylose starch [9], carbomer [10] and hypromellose [11–15]) can be used. Insoluble in EtOH, they are expected to remain unaffected when consumed together with alcohol.

Currently, only one multiple unit dosage form is available that can withstand the influence of alcohol and remain intact in the course of the drug release process. It comprises theophylline pellets coated with Aquacoat® ARC (Alcohol Resistant Coating), which consists of guar gum blended with Aquacoat® ECD (Ethylcellulose Aqueous Dispersion) [17]. Insoluble in alcohol, guar gum acts as a protective layer for the alcohol-soluble ethylcellulose, leaving the controlled-release film intact. Similar controlled-release drug rates were obtained at all tested EtOH concentrations levels (10%, 20%, 40%), confirming the robustness of the coating system [17].

However, to our knowledge, no literature exists concerning the development of uncoated alcohol-resistant multiple unit dosage forms with sustained-release. To fill this gap, in this study we investigated the influence of ethanol on the *in vitro* drug release behavior of hot-melt extruded pellets. Hot-melt extrusion (HME) is a promising technology for the preparation of alcohol-resistant controlling dosage forms. For example, Roth et al. developed the innovative sustained-release Verapamil Meltrex® formulation [18]. The *in vitro* dissolution studies indicated that ethanolic media (5%, 20% and 40% (v/v)) did not affect the drug release rate after 8 h in dissolution media. The authors concluded that the melt-extruded tablets remained intact in the *in vitro* environment and no dose dumping occurred [18].

The hot-melt extruded pellets prepared in our study were composed of the well-characterized analgesic and antipyretic drug paracetamol and the opioid analgesic drug codeine phosphate as model active pharmaceutical ingredients (APIs) and vegetable calcium stearate (CaSt) as a matrix carrier. Being a mixture of water-insoluble calcium salts of stearic and palmitic acid, CaSt is primarily used as a lubricant in tablet and capsule formulations [19]. However, Roblegg et al. demonstrated that CaSt could be used as a pelletisation matrix carrier for spherical slow-release pellets using the wet extrusion/spheronisation technique [20]. Another study by Roblegg et al. established that controlled-release spherical CaSt pellets could be produced via HME [21]. It was demonstrated that CaSt retarded the drug release to a significant extent and by adding plasticizers the *in vitro* release profile could be tailored as desired [21]. Due to its hydrophobic nature, CaSt is insoluble in water and ethanol and is a promising matrix system for alcohol-resistant formulations.

In the current study, two ethanol- and water-insoluble solid lipids (Compritol® and Precirol®), which are suitable for hot-melt extrusion [22,23] were incorporated to form a robust/compact multiple unit dosage form resistant to ethanol. As calcium stearate shows a very high melting point, it is not expected to melt during HME. Hence, the low melting lipids Compritol® and Precirol® were incorporated which melt during the process and therefore, act as binders. All formulations were tested regarding their release characteristics in the presence of ethanol. The main goal was to achieve a better understanding of how alcohol interacts with the formulation, which is the basis for a rational formulation design. To that end, media uptake and wetting behavior upon exposure to ethanolic media were examined. Furthermore, the pellet surface properties and internal morphology were studied via scanning electron microscopy (SEM).

2. Materials and methods

2.1. Materials

Paracetamol and codeine phosphate hemihydrates donated by G.L. Pharma GmbH, Lannach, Austria were used as model APIs. The matrix carrier system was vegetable calcium stearate (stearic acid 44% and palmitic acid 54%, EP) purchased from Werba-Chem GmbH, Vienna, Austria. The solid lipids Precirol® ATO 5 (glycerol distearate) and Compritol® 888 ATO (glycerol dibehenate) were supplied by Gattefossé, Weil am Rhein, Germany. The *in vitro* drug release studies were carried out with 0.1 N hydrochloric acid (HCl) and a trisodiumphosphate-dodecahydrate buffer purchased from Merck, Darmstadt, Germany. For the dose-dumping studies, absolute ethanol (EP) was obtained from VWR International, Darmstadt, Germany. The mobile phase for the reversed phase high performance liquid chromatography (HPLC) consisted of ammonium hydrogenphosphate and ammonium dihydrogenphosphate (Fluka, Sigma Aldrich Chemicals, St. Louis, USA), phosphoric acid (85%, VWR international, Darmstadt, Germany) and methanol (LiChrosolv® Reag., EP, VWR International, Darmstadt, Germany).

2.2. HME process

The powder mixtures for HME were obtained by blending the matrix carrier CaSt and the model drugs paracetamol and codeine phosphate with each of the solid lipids in a turbula mixer at 60 Hz for 20 min (Turbula® TypT2F, Turbula System Schatz, Willy Bachofen AG, Muttenz, Switzerland). The powder blend was transferred into a dosing device (K-Tron, Niederlenz, Switzerland) and gravimetrically fed into a co-rotating twin-screw extruder (ZSK 18, Coperion GmbH, Stuttgart, Germany) with a length-to-diameter ratio (L/D) of 40. The screws were located inside of a cylindrical barrel composed of 10 individually-controllable heating sections. The chosen temperature profiles of all barrel zones are listed in Table 1. Pellets were made directly with our in-house developed hot-die cutter [24]. To produce suitable extruded strands via hot die-face pelletizing, the formulations were extruded at temperatures ranging from 75 to 130 °C (depending on the formulation). The screw speed was set to 200 rpm for all experiments and the throughput of the extruder was 0.5 kg/h. The molten material was extruded through a die plate with a diameter of 1.0 mm. Subsequently, homogeneous strands were cut directly at the die face using a hot die-face pelletizer (Automatik Plastics Machinery GmbH, Großostheim, Germany) with two rotating knives and immediately air-cooled. To obtain pellets in the desired size range, the rotational speed of the knives was set manually to 1200–1300 (depending on the formulation). An overview of the formulations and the processing parameters is given in Table 1.

2.3. Characterization of powder substances and pellets

2.3.1. Differential scanning calorimetry

Thermal properties of the pure powder substances and the hot-melt extruded pellets were characterized using a differential scanning calorimeter (DSC 204F1 Phoenix®, Netzsch GmbH, Selb, Germany). Samples of about 6–9 mg were weighed into aluminum crucibles, which were sealed and pierced. The model APIs and CaSt were scanned between 25 to 200 °C at a heating rate of 5 K/min, with pure nitrogen as the purge gas at a flow rate of