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Novel semisolid SNEDDS based on PEG-30-di-(polyhydroxystearate): Progesterone incorporation and in vitro digestion

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ABSTRACT

The aim of this work is to study the digestibility of PEG-30-di-(polyhydroxystearate) (Cithrol® DPHS) and its semisolid novel self-nanoemulsifying drug delivery systems (SNEDDS). Furthermore, the SNEDDS-mediated solubility enhancement of the poorly water-soluble drug Progesterone was evaluated in different media. Additionally, the impact of digestion on Progesterone solubilization was investigated in vitro by a pancreatin digestion assay. The Progesterone-loaded semisolid self-nanoemulsifying formulation (F2) was comprehensively characterized by photon correlation spectroscopy (PCS), differential scanning calorimetry (DSC), powder X-ray diffraction (PXRD) and Fourier transform infrared spectroscopy (FTIR). SNEDDS were able to enhance the equilibrium solubility of Progesterone at various media. Only a minor part of Cithrol® DPHS was digested by pancreatin (less than 6%). Furthermore, protection of Progesterone against digestion-mediated precipitation was observed. Therefore, DPHS containing SNEDDS are attractive candidates for the development of bio robust drug delivery systems for the oral delivery of poorly soluble drugs.

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1. Introduction

Self-nanoemulsifying drug delivery systems (SNEDDS) are lipid formulations that have drawn considerable attention and ultimately therapeutical and commercial success in the oral delivery of poorly water-soluble drugs (PWSDs). They provide the PWSDs in the form of solubilized nanodispersions (Williams et al., 2013). Accordingly, the rate-limiting step of PWSDs dissolution is bypassed. Nevertheless, SNEDDS are typically filled in soft gelatin capsules, which might cause the following problems: interaction with the capsule shell, instability, higher production cost and possible drug precipitation (Chen et al., 2010; Gullapalli, 2010; Serajuddin et al., 1986; Zhang and DiNunzio, 2012). Therefore, alternative formulation strategies, e.g., the inclusion of SNEDDS into a solid or semisolid dosage form are desirable; nonetheless, very challenging. One approach is the incorporation of the liquid system into a hydrophilic polymer matrix such as PEG (Li et al., 2009) or the use of solid polymeric amphipiles such as Poloxamer 188 (Shah and Serajuddin, 2012). Another approach is the use of semisolid or solid lipids such as Acconon® C-44 (Patel et al., 2012b), Acconon® C-50 (Patel et al., 2012a), Cithrol® DPHS (Hassan et al., 2014), Gelucire® 50/13 (Patel et al., 2012a) and Gelucire® 44/14 (Breitkreitz et al., 2013; Fernandez et al., 2008). Other approaches include extrusion/spheronization (Abdalla and Mäder, 2007), melt granulation (Nanda Kishore et al., 2014), adsorption to solid carriers (Agarwal et al., 2013), spray and freeze drying (Singh et al., 2013), rotary evaporation (Myers and Shively, 1992) and fluid-bed coating (Krupa et al., 2014).

Semisolid SNEDDS are more advantageous than the liquid ones. They have higher viscosity that usually affords high drug stability (Singh et al., 2014) and may protect the PWSDs against precipitation upon minor change in the product temperature. In our previous study, we have reported the novel use of PEG-30-di-(polyhydroxystearate) as a lipophilic excipient in the formulation of SNEDDS (Hassan et al., 2014). We have successfully developed semisolid SNEDDS based on Cithrol® DPHS (DPHS), Capmul® MCM

Abbreviations: 12-HSA, 12-hydroxystearic acid; CEH, carboxyl ester hydrolase; DPHS, Cithrol® DPHS; DSC, differential scanning calorimetry; ESR, electron spin resonance; FaSSIF, fasted state simulated intestinal fluid; FeSSIF, fed state simulated Intestinal fluid; FTIR, Fourier transform infrared spectroscopy; HPLC, high performance liquid chromatography; HPTLC, high performance thin-layer chromatography; HS15, Kolliphor® HS 15; MCM, Capmul® MCM; PCS, photon correlation spectroscopy; PDI, polydispersity index; PEG, polyethylene glycol; PLA2, phospholipase A2; PLPR2, pancreatic lipase-related protein 2; PWSDs, poorly water-soluble drugs; PXRD, powder X-ray diffraction; rpm, revolutions per minute; SD, standard derivation; SDM, solvent displacement method; SNEDDS, self-nanoemulsifying drug delivery systems; USP, United States pharmacopeia; UTM, Ultra-Turrax® method.

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(MCM) and Kolliphor® HS 15 (HS15). All formulations were able to produce nanodispersions with an average droplet size diameter below 25 nm. Although formulations were semisolid at room temperature, they have shown high molecular mobility upon dispersion in aqueous media at body temperature, which is very essential for the in vivo performance of the SNEDDS.

Oral administration of lipids stimulates the secretion of gastric lipase from the gastric mucosa, with the consequent secretion of pancreatic lipase and co-lipase from the pancreas along with other esterases such as phospholipase A2 (PLA2), carboxyl ester hydrolase (CEH) and pancreatic lipase related protein 2 (PLPRP2). Most of the lipid excipients are esters such as glycerides (MCM), polyethylene glycol esters of fatty acids (HS15 and DPHS), polysorbates and phospholipids. Ester bonds are generally potential substrates to lipolytic enzymes. For example, triglycerides are hydrolyzed into two free fatty acids and 2-monoacylglycerides (N'Goma et al., 2012). The breakdown products are then incorporated in the bile mixed micelles. However, lipid digestion might decrease the solubilization capacity of the carrier, and – as a consequence – drug precipitation might occur. Therefore, in vitro lipid digestion studies, using biorelevant dissolution media containing enzymes and naturally occurring surfactants such as bile salts and lecithin, are recommended to evaluate the performance of SNEDDS (Christophersen et al., 2014; Fatouros and Mullertz, 2008; Phan et al., 2014; Thomas et al., 2012).

The most important methods that are used to evaluate the in vitro lipid digestibility are related to pH-stat measurements and high performance thin layer chromatography (HPTLC) combined with spectrodensitometry (Fatouros and Mullertz, 2008; Williams et al., 2012b). The pH-stat method is the simplest and the most widely used method for evaluation of in vitro lipid digestion. However, this method relies on the ionization state of the fatty acids. The titration should be carried out at pH values, which are at least 2 units higher than the pK_a of the acid. Long chain fatty acids (e.g., C16 and C18) might be underestimated due to their higher apparent pK_a values and partial localization in more lipophilic environments, which makes them non accessible for titration. Therefore, back titration at higher pH values is sometimes used to minimize these problems (Williams et al., 2012b). HPTLC combined with spectrodensitometry provides a better overview of all digestion products such as fatty acids, monoglycerides, diglycerides, triglycerides as well as other digestion products (e.g., PEG esters). On the other side, pH-stat combined with the back titration method provides only the total fatty acid concentration (Sek et al., 2001, 2002). A direct measurement of lipid digestion by optical methods is difficult due to the complex and turbid nature of pancreatin. However, a continuous monitoring of digestion induced translocation of model compounds has been described using electron spin resonance (ESR) (Abdalla and Mäder, 2009; Noack et al., 2012). The beauty of a direct measurement is counterbalanced by the fact that ESR requires paramagnetic molecules and therefore no real drugs can be monitored.

Progesterone was selected as a PWSD model with a log P of 3.87 (Bard et al., 2008). Progesterone is a steroid that is used in the treatment of many gynecological disorders (McAuley et al., 1996). It occurs in 2 polymorphic forms: form 1 (α-form) and form 2 (β-form) (Araya-Sibaja et al., 2014). Oral Progesterone administration is associated with poor bioavailability because of its very low water solubility as well as extensive hepatic first-pass metabolism (Sitruk-Ware et al., 1987). Accordingly, Progesterone is a good candidate for SNEDDS-mediated bioavailability enhancement.

The aim of this study is to evaluate the digestibility of the novel PEG-30-di-(polyhydroxystearate) based SNEDDS and their excipients, with particular interest on DPHS digestibility. The assessment was done by means of an in vitro pancreatin digestion assay under both fasted (FaSSIF) and fed (FeSSIF) states. Both pH-stat combined with back titration and HPTLC combined with spectrodensitometry were used in the digestibility evaluation. Furthermore, the Progesterone loading was studied in the single excipients (DPHS, MCM and HS15) as well as in their SNEDDS mixtures. Moreover, the SNEDDS-mediated enhancement of Progesterone equilibrium solubility was evaluated in different media. The droplet size distributions were measured by static or dynamic light scattering. Differential scanning calorimetry (DSC) and Fourier transform infrared spectroscopy (FTIR) were used to determine the possible SNEDDS–Progesterone interactions. Powder X-ray diffraction (PXRD) was used to evaluate the physical state of the Progesterone-loaded SNEDDS.

2. Materials and methods

2.1. Materials

Cithrol® DPHS was kindly provided by Croda GmbH, Nettetal, Germany. Kolliphor® HS 15 was a gift from BASF AG, Ludwigshafen, Germany. Capmul® MCM was kindly supplied by Abitec Corporation, Janesville, WI, USA. Progesterone, porcine bile extract and porcine pancreatin powder (4xUSP specification activity) were purchased from Sigma–Aldrich, Steinheim, Germany. Phospholipon® 90G (purified phosphatidylcholine from soybean lecithin) was purchased from Lipoid, Ludwigshafen, Germany. Titrisol® (standard sodium hydroxide solution, 1 M) was purchased from Merck, Darmstadt, Germany. Acetonitrile HPLC was purchased from VWR, Darmstadt, Germany. All other materials were of analytical grade and were used as received.

2.2. Formulation preparation

DPHS, MCM and HS15 were molten together and mixed (Table 1). The mixtures were cooled down to room temperature and allowed to equilibrate for 24 h at 23 °C prior to further analysis (Hassan et al., 2014).

2.3. In vitro lipid digestion

2.3.1. Used media

Simulated intestinal fluids are composed of Sørensen's phosphate buffer pH 6.8 (35.6 mM potassium dihydrogen phosphate and 31.1 mM disodium monohydrogen phosphate dihydrate), 150 mM sodium chloride and 5 mM calcium chloride. FaSSIF was supplemented with 5 mM bile extract and 1.25 mM phospholipids while FeSSIF was supplemented with 15 mM bile extract and 3.75 mM phospholipids. As an enzyme source, 450 U/ml of porcine pancreatin was used (Abdalla et al., 2008).

2.3.2. Preparation of Cithrol® DPHS dispersions

Two methods were used to prepare DPHS dispersions: the Ultra-Turrax® method (UTM) and the solvent displacement method (SDM).

2.3.2.1. Ultra-Turrax® method (UTM). Molten DPHS was mixed with Sørensen's phosphate buffer pH 6.8 using a rotor-stator mixer (Ultra-Turrax® T18 basic, IKA, Staufen, Germany) operated at 24,000 rpm for 5 min at room temperature.

Table 1
Composition of the PEG-30-di-(polyhydroxystearate) SNEDDS formulations (m%).

Formulation code	Cithrol® DPHS	Capmul® MCM	Kolliphor® HS 15
F1	20	20	60
F2	26.67	13.33	60
F3	30	10	60

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