European Journal of Pharmaceutical Sciences 108 (2017) 62–70

Contents lists available at ScienceDirect

European Journal of Pharmaceutical Sciences

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

Monoacyl phosphatidylcholine inhibits the formation of lipid multilamellar structures during *in vitro* lipolysis of self-emulsifying drug delivery systems

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ARTICLE INFO

Article history:
Received 22 June 2016
Received in revised form 21 November 2016
Accepted 22 November 2016
Available online 24 November 2016

Keywords:
Monoacyl phosphatidylcholine
Self-emulsifying drug delivery systems
In vitro lipolysis
Colloidal structures
Small-angle X-ray scattering
Cryogenic transmission electron microscopy

ABSTRACT

The colloidal structures formed during lipolysis of self-emulsifying drug delivery systems (SEDDS) might affect the solubilisation and possibly the absorption of drugs. The aim of the current study is to elucidate the structures formed during the *in vitro* lipolysis of four SEDDS containing medium-chain glycerides and caprylocaproyl polyoxyl-8 glycerides (Labrasol), with or without monoacyl phosphatidylcholine (MAPC). *In situ* synchrotron small-angle X-ray scattering (SAXS) was combined with *ex situ* cryogenic transmission electron microscopy (cryo-TEM) and dynamic light scattering (DLS) to elucidate the generated structures. The SAXS scattering curves obtained during the lipolysis of MAPC-free SEDDS containing 43–60% w/w Labrasol displayed a lamellar phase peak at $q = 2.13\ nm^{-1}$ that increased with Labrasol concentration, suggesting the presence of multilamellar structures (MLS) with a d-spacing of 2.95 nm. However, SEDDS containing 20–30% w/w MAPC did not form MLS during the lipolysis. The cryo-TEM and DLS studies showed that MAPC-free SEDDS formed coarse emulsions while MAPC-containing SEDDS formed nanoemulsions during the dispersion in digestion medium. From the first minute and during the entire lipolysis process, SEDDS both with and without MAPC generated uni-, bi-, and oligo-lamellar vesicles. The lipolysis kinetics in the first minutes of the four SEDDS correlated with an increased intensity of the SAXS curves and the rapid transformation from lipid droplets to vesicles observed by cryo-TEM. In conclusion, the study elucidates the structures formed during *in vitro* lipolysis of SEDDS and the inhibitory effect of MAPC on the formation of MLS.

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1. Introduction

Poorly water-soluble drugs often have low and variable oral absorption as a consequence of their limited solubility and slow dissolution rate in the aqueous environment of the gastrointestinal tract. The successful use of lipid-based formulations (LBF) to enhance the absorption of these compounds has been previously described (Müllertz et al., 2010). Among the LBF, self-emulsifying drug delivery systems (SEDDS) are of special interest since they have been shown to efficiently improve the oral bioavailability of several poorly-water soluble drugs (Kovarik et al., 1994; Larsen et al., 2008; Nielsen et al., 2008). SEDDS often contain synthetic surfactants, which may lead to irritation of the gastrointestinal mucosa (Hauss, 2007). It is therefore important to reduce the amount of synthetic surfactants in SEDDS (while maintaining their self-emulsification capacity) by using natural surfactants. Monoacyl phosphatidylcholine (MAPC) (Table 1) (also known as lyso-phosphatidylcholine) is a natural surfactant present in the human intestinal tract as a digestion product of phospholipids (van Hoogevest and Wendel, 2014). MAPC enhanced the lymphatic transport of α-tocopherol from an oil-in-water emulsion in rats (Koo and Noh, 2001). Soybean MAPC has been used in medium-chain (MC) glycerides-based SEDDS to limit the concentration of synthetic surfactants and reduce the nanoemulsion droplet sizes formed when the formulations were dispersed in simulated gastric and intestinal fluids media (Tran et al., 2016).

One of the mechanisms by which LBF enhance drug solubilisation and oral absorption is stimulating the secretion of digestive juices thus increasing the concentration of bile salts, phospholipids and cholesterol in the intestinal lumen (Kossena et al., 2007). These endogenous substances combine with lipids and lipid digestion products (such as fatty acids and monoglycerides) to form complex colloidal structures (such as mixed-micelles, vesicles and liquid crystalline phases). These colloidal structures impact the distribution and solubilisation of drugs in the digestive environment (Kossena et al., 2004; Kossena et al., 2005). Consequently, the intermediate colloidal phases originating from lipid digestion play an important role in the solubilisation and possibly oral

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http://dx.doi.org/10.1016/j.ejps.2016.11.022
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Table 1
Principal components of the used excipients and their chemical structures.

Excipient	Composition	Chemical structure of principal components
Captex 300	TG of predominantly C8:0 (70%) and C10:0 FA.	
Capmul MCM EP	MG (45–75%) and DG (20–50%) predominantly of C8:0 (50–90%) and C10:0 FA (10–50%).	
Labrasol	PEG-8 monoester, diesters of C8:0/C10:0; MG, DG, TG of C8:0/C10:0 FA; Free PEG residue (Jannin et al., 2014)	
Lipoid S LPC 80	MAPC (80%) and PC (13%) of C18:2 (48–56%), C16:0 (20–27%), C18:0 (5–8%), C18:1 (7–9%) FA.	

Abbreviations: DG: diacylglycerides; FA: fatty acid; MAPC: monoacyl phosphatidylcholine; MG: monoacylglycerides; PC: phosphatidylcholine; PEG: polyethylene glycol; TG: triacylglycerides.

absorption of drugs. Thus, a thorough investigation into the colloidal systems formed during digestion is believed to be required for a rational lipid-based formulation design.

Considering the role of lipolysis products in drug solubilisation, simple dissolution or dispersion tests are often inadequate to evaluate LBF performance (Larsen et al., 2011). *In vitro* lipolysis models have therefore been developed, simulating the conditions of lipid digestion in the human intestine, to study the generated colloidal structures and the drug solubilisation and partitioning between the different phases (Christensen et al., 2004). Fatouros et al. (2007a, 2007b) have used cryogenic transmission electron microscopy (cryo-TEM) and small-angle X-ray scattering (SAXS) to study the structural evolution of SEDDS containing sesame oil, Maisine 35-1, Cremophor RH40 and ethanol (30:30:30:10% w/w) during the *in vitro* lipolysis. In these studies, spherical and elongated unilamellar vesicles were observed under the cryo-TEM and lamellar and inverse hexagonal phases were identified by the SAXS (Fatouros et al., 2007a, 2007b). Even though these studies have shown the likely presence of nanostructures during lipolysis, the experiments were conducted *ex situ*. Consequently, it is difficult to draw definitive conclusions about these findings, especially because lipid digestion is a dynamic process with continuous evolution of the colloidal phases. *In situ* SAXS was used by Salentinig et al. (2011) to study the colloidal structures formed during the digestion of triolein, which transformed from oil droplets to micellar cubic, inverse hexagonal, and bicontinuous cubic liquid crystalline phases during digestion (Salentinig et al., 2011). Subsequently, synchrotron SAXS was applied to lipolysis studies of SEDDS due to its shorter acquisition time, allowing real-time monitoring of structural evolution (Phan et al., 2013, 2015; Warren et al., 2011).

Considering the above-mentioned potential use of MAPC in SEDDS and the importance of the nature of the colloidal systems during lipolysis, the aim of the present work is to elucidate the structures formed during the lipolysis of SEDDS both with and without MAPC. For that, *in situ* synchrotron SAXS coupled to the *in vitro* lipolysis model and combined with *ex situ* cryo-TEM and dynamic light scattering (DLS) were used.

2. Materials and methods

2.1. Materials

Lipoid S LPC 80 (LPC) (from soybean, containing 80.8% MAPC and 13.2% phosphatidylcholine (PC)) and Lipoid S PC (from soybean, containing 98.0% PC) were kindly donated by Lipoid GmbH (Ludwigshafen am Rhein, Germany). Captex 300 (Captex) (glyceryl tricaprylate/tricaprate) and Capmul MCM EP (Capmul) (glyceryl monocaprylate) were obtained from Abitec (Columbus, OH, USA). Labrasol (PEG-8 caprylocaproyl glycerides) was kindly provided by Gattefossé (Saint-Priest, France). Pancreatin from porcine pancreas (8 × USP specifications), sodium taurodeoxycholate (NaTDC) hydrate (>95% pure), tris(hydroxymethyl)aminomethane (Tris), maleic acid and 4-bromophenylboronic acid (4-BPB) (≥95.0% pure) were purchased from Sigma-Aldrich (St Louis, MO, USA). Sodium chloride was purchased from VWR (Radnor, PA, USA). Sodium hydroxide pellets were obtained from Merck (Darmstadt, Germany). Water was purified by an SG Ultraclear water system (SG Water GmbH, Barsbüttel, Germany).

2.2. Methods

2.2.1. Preparation of formulations

The chemical structures and the amount of excipients used in each investigated SEDDS are shown in Tables 1 and 2. The two MAPC-containing SEDDS are designated F20 and F30 (the number corresponds to the percentage of LPC in the SEDDS). The two MAPC-free SEDDS are designated F0 and F30*; F0 contains a Labrasol amount equal to the total amount of Labrasol and LPC in F20 or F30, whereas F30* contains the same glycerides:Labrasol ratio as F30. Capmul was melted at 50 °C and homogenized prior to use. All formulations were prepared by weighing and mixing all components in a glass vial for 4 h at 45 °C. The formulations were allowed to equilibrate at room temperature overnight before further experiments to ensure excipient homogeneity.

2.2.2. In vitro lipolysis model

The experimental set-up consisted of a pH-stat apparatus (Metrohm AG, Herisau, Switzerland), containing a Titrando 842, an 804 Ti Stand, an

Table 2
Composition of the SEDDS used in the *in vitro* lipolysis experiments.

Formulation	Excipients (g)				
	Captex 300	Capmul MCM EP	Labrasol	Lipoid S LPC 80	TOTAL
F0	0.2	0.2	0.6	–	1.0
F20	0.2	0.2	0.4	0.2	1.0
F30	0.2	0.2	0.3	0.3	1.0
F30*	0.2	0.2	0.3	–	0.7

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