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Formulation and characterization of self-nanoemulsifying drug delivery systems containing monoacyl phosphatidylcholine

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ABSTRACT

The study investigated the use of monoacyl phosphatidylcholine (MAPC) in self-nanoemulsifying drug delivery system (SNEDDS). A D-optimal design was used to generate two sets of formulations containing long-chain (LC) or medium-chain (MC) glycerides, caprylocaproyl macrogol-8 glycerides (Labrasol), Lipoid S LPC 80 (LPC) (80% MAPC) and ethanol. The formulations were characterized using dynamic light scattering, microscopy, *in vitro* lipolysis and viscometric measurements. All LC formulations within the investigated range were predicted to generate polydisperse emulsions while MC formulations generated nanoemulsions with droplet sizes from 23 to 167 nm. Using LPC in MC formulations reduced the nanoemulsion droplet sizes in simulated gastric and intestinal media. The nanoemulsion droplet size of MC SNEDDS containing LPC was not affected by gastrointestinal pH, while the zeta potentials increased at low pH. During *in vitro* lipolysis, less fatty acids were released when LPC was incorporated into the formulations (2.05 ± 0.02 mmol reduced to 1.76 ± 0.05 mmol when incorporating 30% LPC). Replacing Labrasol by LPC increased the formulation dynamic viscosity from 57 ± 1 mPa s (0% LPC) to 436 ± 8 mPa s (35% LPC) at 25 °C, however, this did not considerably prolong the formulation dispersion time. In conclusion, MC SNEDDS containing LPC are promising formulations when desiring to reduce the amount of synthetic surfactants and possibly modify the digestion rate.

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1. Introduction

The majority of new low-molecular-weight chemical entities in the drug discovery programs of the pharmaceutical industry exhibit insufficient aqueous solubility to ensure adequate oral absorption and therefore often provide poor and unpredictable oral bioavailability (Lipinski, 2000; Lipinski et al., 2012). For several decades, lipid-based drug delivery systems have been developed to overcome this problem by presenting lipophilic drugs in solubilized form in the gastro-intestinal tract, in order to avoid the dissolution process, which is often slow or incomplete with a conventional solid dosage form (Porter et al., 2007). Some other bioavailability enhancing mechanisms provided by lipid-based drug delivery systems include prolonging gastric residence time (Van Citters and Lin, 1999), stimulating lymphatic transport (Caliph et al., 2000), increasing intestinal permeability (Buyukozturk et al., 2010; Gupta et al., 2011), reducing intestinal metabolism (Patel and Brocks, 2009) and inhibiting P-glycoprotein activity (Constantinides and Wasan, 2007). Despite these acknowledged advantages, the emulsification of lipid-based formulations often depends on the variable human digestive environments, rendering the dissolution and absorption profile of drugs unpredictable and poorly reproducible (Porter et al., 2007). Using self-nanoemulsifying drug delivery systems (SNEDDS) to form nanoemulsions in gastrointestinal media can overcome these inter- and intra-subject variations (Pouton, 2000). Previous research has shown that SNEDDS reduce the variability in oral absorption and provide higher oral bioavailability for cyclosporine A (Kovarik et al., 1994), probucol (Nielsen et al., 2008), and cinnarizine (Larsen et al., 2013) compared to lipid-based drug delivery systems generating coarse emulsions upon dispersion.

Most SNEDDS are comprised of triglycerides, hydrophilic surfactants, co-surfactants and cosolvents, allowing self-emulsification and enhancing drug solubilization (Pouton, 2000). To date,

Abbreviations: Cryo-TEM, cryogenic transmission electron microscopy; DoE, design of experiments; $FaSSGF_{TDC}$, fasted-state simulated gastric fluid containing sodium taurodeoxycholate; FaMIF, fasted-state median intestinal fluid; LC, long-chain; LPC, Lipoid S LPC 80; MAPC, monoacyl phosphatidylcholine; MC, medium-chain; PC, phosphatidylcholine; SNEDDS, self-nanoemulsifying drug delivery systems.

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most surfactants used in SNEDDS are synthetic and potentially provoke irritancy to cell membranes of the digestion tract, especially in children (Gloxhuber, 1974; Attwood and Florence, 1983). Replacing or reducing these synthetic surfactants by a natural surfactant is an interesting option for future development of SNEDDS, particularly as a pediatric dosage form.

Monoacyl phosphatidylcholine (MAPC) (Fig. 1), also known as lyso-phosphatidylcholine, is generated from the digestion of phosphatidylcholine in the upper small intestine and absorbed intact into the enterocytes by passive diffusion (Carey et al., 1983; Tso, 1985). As a soluble amphiphilic lipid (Class IIIA), MAPC can form large micelles in aqueous media (Small, 1968). Soybean MAPC effectively enhances emulsion stability when being combined with nonionic surfactants such as glyceryl monostearate and sorbitane monostearate (Fujita et al., 1993). MAPC also promoted the permeability of 1-deamino-8-D-arginine-vasopressin when being tested in a Caco-2 cell monolayer (Hovgaard et al., 1995) and that of dextran and bovine serum albumin when being tested in a rat model (Tagesson et al., 1985). Using soybean MAPC in SNEDDS as a surfactant could be of special interest, when aiming to reduce the concentration of synthetic surfactants while maintaining adequate emulsification capacity, but, to the knowledge of the authors, this has not been investigated yet. The aims of the current study were therefore (1) to investigate the formulation of SNEDDS containing soybean MAPC using a design of experiments (DoE) approach and (2) to characterize SNEDDS in terms of dispersion properties, *i.e.* the emulsion droplet size and zeta potential in biorelevant media; *in vitro* lipolysis profile; and viscometric properties, when gradually replacing the synthetic surfactant Labrasol by MAPC.

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 provided by Lipoid GmbH (Ludwigshafen am Rhein, Germany). Soybean oil, sodium taurodeoxycholate hydrate (NaTDC) (>95% pure), 2-(*N*-morpholino) ethanesulfonic acid (MES) hydrate, MES sodium salt, Trizma maleate, and pancreatin from porcine pancreas were purchased from Sigma-Aldrich (St. Louis, MO, USA). Maisine 35-1 (Maisine) (glyceryl monolinoleate) and Labrasol (caprylocaproyl macrogol-8 glycerides) were gifts from Gattefossé (Saint-Priest, France). Captex 300 (Captex) (glyceryl tricaprylate/tricaprate) and Capmul MCM EP (Capmul) (glyceryl monocaprylate) were kindly provided by Abitec (Columbus, OH, USA). Absolute ethanol (99.9%) and sodium chloride were obtained from VWR (Radnor, PA, USA). Water was purified by a SG Ultraclear water system (SG Water GmbH, Barsbüttel, Germany).

2.2. Methods

2.2.1. Design of experiments

A D-optimal experimental design of 13 experiments, including 3 center points, was generated by MODDE 10.1.0 software (Umetrics, Sweden) for two formulation sets containing 40% mixed glycerides, 30–55% Labrasol, 0–25% LPC, and 0–10% ethanol. Table 1 shows the composition of the DoE formulations. A classical mixture design was not chosen because Labrasol, LPC and ethanol ranges are different (Eriksson et al., 2008). One formulation set was based on long-chain (LC) glycerides (soybean oil:Maisine (1:1 w/w)), called “LC formulation set” hereafter, while the other set was based on medium-chain (MC) glycerides (Capmul:Captex (1:1 w/w)), and was called “MC formulation set” hereafter. All formulations were dispersed in a fasted-state median intestinal fluid (FaMIF) (Madsen et al. 2016) (Table 2) prepared based on the median values of pH, bile salts and phospholipid concentrations, osmolarity and buffer capacity of human fasted-state intestinal fluids, as described by Bergstrom et al. (2014). The droplet size of the obtained emulsions was measured using dynamic light scattering (DLS) (described below). The matrix of the Labrasol, LPC and ethanol concentrations was correlated to the matrix of the droplet sizes by partial least square regression (Lundstedt et al., 1998) using the MODDE 10.1.0 software. The model quality was evaluated based on the goodness of fit (R^2) and goodness of prediction (Q^2). A R^2 close to 1 refers to a model of good fit; a Q^2 close to 1 refers to excellent prediction power; and Q^2 larger than 0.5 refers to good prediction power (Eriksson et al., 2008).

2.2.2. Characterization of SNEDDS containing LPC

2.2.2.1. Droplet size and zeta-potential measurements. The investigated dispersions were prepared by adding the formulations to the biorelevant media at a ratio of 1:200 under gentle overhead stirring using a rotator (Intelli-Mixer RM-2M, In Vitro, Denmark) at 20 rpm and 37 °C for 5 min. The biorelevant media used were the fasted-state simulated gastric fluid using NaTDC ($FaSSGF_{TDC}$) (instead of using sodium taurocholate as in the original FaSSGF (Galia et al., 1998)) or FaMIF. Table 2 shows the composition of $FaSSGF_{TDC}$ and FaMIF. Preliminary experiments showed that pepsin at the concentration of 0.1 mg/mL did not influence the droplet size and zeta potential of the dispersion, but interfered with the measurement quality by making the medium turbid. Pepsin was therefore eliminated from the $FaSSGF_{TDC}$ used.

The droplet size of the dispersion was measured by DLS and the zeta potential was measured by the mixed-mode measurement phase analysis light scattering technology (M3-PALS) at 37 °C using a Zetasizer Nano ZS (Malvern, UK). The effect of pH on the droplet size and zeta potential was investigated by measuring droplet size and zeta potential of the nanoemulsions formed upon dispersion (1:200) in $FaSSGF_{TDC}$ or FaMIF at pH 1.6, 3.0, 5.0, 6.6 and 9.0. For all measurements, three independent samples of each formulation were investigated.

2.2.2.2. Microscopy studies. The systems formed when dispersing the formulations from the DoE in FaMIF were observed by optical microscopy at a magnification of 400× (Zeiss Axiolab, Carl Zeiss GmbH, Germany) and cryogenic transmission electron microscopy (Cryo-TEM). For Cryo-TEM observation, 3 μL of the samples were applied on Lacy 3000 holey carbon film grids (Ted Pella Inc., CA, US). The grids were blotted in a Vitrobot automated vitrification device (FEI, Eindhoven, The Netherlands) under controlled environmental conditions (25 °C, 100% relative humidity), then automatically plunged into liquid ethane to rapidly freeze the samples and transferred to liquid nitrogen (approximately −174 °C). The frozen samples were then transferred to a Gatan 626 cryoholder (Gatan Inc., Warrendale, PA, USA) coupled to a FEI

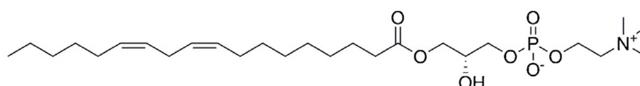

Fig. 1. Chemical structure of MAPC.

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