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SNEDDS containing bioenhancers for improvement of dissolution and oral absorption of lacidipine. I: Development and optimization

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ABSTRACT

The aim of this study was to develop and optimize SNEDDS formulations containing surfactants reported to be bioenhancers for improvement of dissolution and oral absorption of lacidipine (LCDP). Preliminary screening was carried out to select proper components combination. D-optimal mixture experimental design was applied to optimize a SNEDDS that contains a minimum amount of surfactant, a maximum amount of lipid, and possesses enhanced emulsification and dissolution rates. Three formulation variables; the oil phase X_1 (a mixture of Labrafil®/Capmul®), the surfactant X_2 (a mixture of Cremophor®/Tween® 80) and the co-surfactant X_3, were included in the design. The systems were assessed for droplet size, light absorbance, optical clarity, drug release and emulsification efficiency. Following optimization, the values of formulation components (X_1, X_2, and X_3) were 34.20%, 40.41% and 25.39%, respectively. There is a good correlation between light absorbance and droplet size analysis of diluted SNEDDS (R^2 = 0.883). Transmission electron microscopy demonstrated spherical droplet morphology. The stability of the optimized formulation was retained after storage at 40 °C/75% RH for three months. The optimized formulation of LCDP showed a significant increase in dissolution rate compared to the drug suspension under the same conditions. Our results proposed that the optimized SNEDDS formulation, containing bioenhancing surfactants, could be promising to improve oral absorption of LCDP.

1. Introduction

Lacidipine (LCDP) is a calcium channel blocker developed for oral administration and widely used in therapy since the early 1990s. LCDP is used in the treatment of hypertension and atherosclerosis. It also possesses an antioxidant effect (Lee and Bryson, 1994; McCormack and Wagstaff, 2003). The active Trans form is used in therapy (De Filippis et al., 2002); unfortunately, lacidipine is a highly lipophilic drug of poor water solubility and undergoes extensive first-pass hepatic metabolism with a mean absolute bioavailability of ~10% (range 3–59%). It is completely metabolized in the liver by cytochrome P450 3A4 (CYP3A4) to pharmacologically inactive metabolites (Tang et al., 2008). In spite of the marked role of the drug in hypertension therapy, no reported trials were so far adopted to enhance its oral absorption.

Formulation design can be a useful approach to improve the absorption and thus the oral bioavailability of such drug candidates (Pouton, 2006; Balakrishnan et al., 2009). Nanoemulsions, including self-emulsifying (SEDDS) and self-nanoemulsifying drug delivery systems (SNEDDS) are among the methods used to improve the oral bioavailability of poorly soluble drugs (Kommuru et al., 2001; Hong et al., 2006). SNEDDS comprise isotropic mixtures of natural or synthetic oils with surfactants and co-surfactants. These systems spontaneously emulsify when exposed to GIT fluids to form oil in water nanoemulsion with nanometric droplet size, in the range of 20–200 nm (Mou et al., 2008; Porter et al., 2008). The small droplet size confirms the highly efficient absorption of these oil droplets due to the rapid drug dissolution and release (Rao and Shao, 2008). SNEDDS are characterized by high solvent capacity and excellent stability. In addition, they can improve oral bioavailability through enhancing permeation across the intestinal membrane, reduce or eliminate food effect, solubilization, droplet size reduction and improvement of drug dissolution (Rane and Anderson, 2008; Wasan et al., 2009; Wang et al., 2010). The drug can also be delivered by lymphatic transport through the intestine avoiding the hepatic first-pass metabolism (Porter and Charman, 2001). Furthermore, SNEDDS formulations, containing bioenhancers that contain certain types of surfactants such as Cremophor®, Tween 80® and Labrasol®, are also reported to further improve the bioavailability of absorbed compounds by facilitating transcellular and paracellular absorption. Bioenhancers act also as p-glycoprotein and/or CYP450 enzymes inhibitors decreasing intestinal efflux and drug biotransformation (Yu et al., 1999; Chen, 2008; Elnaggar et al., 2009).

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Labrasol® enhances both membrane permeability and intestinal absorption of cephalexin, a widely used β-lactam antibiotic (Koga et al., 2002) and significantly improves the efficacy of Vancomycin, a water soluble glycopeptide antibiotic with poor absorption characteristics (Prasad et al., 2003).

Development of a pharmaceutical formulation is time consuming and labor intensive. This is especially true for the SNEDDS, because its composition usually is complex, involving multiple components. The application of a mixture experimental (D-optimal) design to pharmaceutical formulation development has been demonstrated to be an efficient and satisfactory method for optimization of the formulation and to acquire the necessary information to understand the relationship between controllable (independent) variables and performance or quality (dependent variables) in a formulation (Gao et al., 2004).

Literature lacks any data about the use of SNEDDS for improvement of the dissolution and oral absorption of LCDP. Thus, the aim of this study was the formulation and optimization of LCDP-loaded SNEDDS containing surfactants reported to be bioenhancers. Experimental mixture design and desirability function were applied to optimize SNEDDS that contain a minimum amount of surfactant, a maximum amount of lipid, and possess enhanced emulsification and dissolution rates. As part of the optimization process, the main effect, interaction effects and quadratic effects of amounts of lipid, surfactant and co-surfactant on drug release, droplet size and emulsification time were investigated. The optimized formulation exhibiting promising in vitro drug dissolution is anticipated to improve oral absorption of the drug. Development and in vivo evaluation of controlled release solid dosage forms of the optimized LCDP formulation for management of hypertension are presently investigated.

2. Materials and methods

2.1. Materials

Lacidipine was kindly supplied by EgyPharm (Egypt). Labrafil® M 1944 CS (Labrafil-M, oleoyl macrogolglycerides), Labrafil® M 2125 CS (Labrafil, linoleoyl macrogolglycerides), Transcutol® P (purified diethylene glycol monoethyl ether), Maisine® 35-1 (glyceryl monolinoleate), Labrasol® (PEG-8 glycol caprylate), Lauroglycol 90 (propylene glycol monolaurate) were kindly obtained from Gattefosse (France). Capmul® MCM C8 (glyceryl monocaprylate) was obtained from Abitec Corp. (Janesville, WI). Miglyol® 812 (caprylic/capric triglyceride) was obtained from Sasol (Witten, Germany). Cremophor® RH 40 (Polyoxyl 40 hydrogenated castor oil) from BASF (Germany). Tween® 80 (polysorbate 80) and HCl were purchased from Merck (Germany). All other chemicals and solvents were of analytical grade and used without further purification.

2.2. Solubility studies

The solubility of LCDP in various oils, surfactants, and co-surfactants was determined. 2 g of each of the selected vehicles were added to each vial containing known excess of LCDP (500 mg). After sealing, the mixtures were shaken at 30 ± 0.5 °C for 48 h in a thermostatically controlled shaking water bath (Model 1083, GLF Corp., Germany). After reaching equilibrium, the mixtures were centrifuged at 3000 rpm for 5 min, followed by filtration through a Millipore membrane filter (0.45 μm).

The filtrate was diluted with chloroform and quantified spectrophotometrically (UV-1601 PC, Shimadzu, Japan) for dissolved LCDP via a validated method at 360 nm using chloroform as a blank. Each experiment was carried out in triplicate.

2.3. Preliminary screening of various surfactants for their emulsifying ability

Emulsification ability of various surfactants was screened according to the method described by Date and Nagarsenker (2007). 300 mg of each surfactant (Labrasol®, Cremophor® and Tween® 80) was added to 300 mg of the oily phase (Labrafil®). The mixtures were gently heated at 50 °C for homogenizing the components. 50 mg of each mixture was accurately weighed and appropriately diluted with double distilled water to yield fine emulsion. The ease of formation of emulsions was monitored by noting the number of volumetric flask inversions required to give uniform emulsion. The resulting emulsions were observed visually for the relative turbidity, then allowed to stand for 2 h and their transmittance was assessed spectrophotometrically (UV-1601 PC, Shimadzu, Japan) at 638.2 nm using double distilled water as blank.

2.4. Construction of ternary phase diagrams

The existence of self-nanoemulsifying oil formulation fields that could self-emulsify under dilution and gentle agitation were identified from ternary phase diagrams of systems containing oil, surfactant and co-surfactant. A series of self-emulsifying systems were prepared in each of the four formulation systems with varying concentrations of oils; Miglyol® and Labrafil®, surfactants; Cremophor® and Tween® 80 and co-surfactants; Transcutol®. For any mixture, the total of surfactant, co-surfactant and oil concentrations always added to 100%.

2 g of each mixture was prepared by the addition of variable proportions of the oil, surfactant and co-surfactant into a 10-mL capped glass vial. The components were mixed by vortex mixer (Paramix II, Julabo, Germany) for 60 s. The efficiency of nanoemulsion formation was assessed by adding 100 mg of each mixture to 20 mL double distilled water, followed by gentle agitation using a magnetic stirrer. The lipid-based formulations were assessed visually according to the rate of emulsification and the final appearance of the emulsion (Date and Nagarsenker, 2007). Only clear or slight bluish dispersions of droplet size 200 nm or lower were considered in the nanoemulsion region of the diagram (Zhang et al., 2008).

2.5. Formulation optimization of LCDP-loaded SNEDDS

The mixture experimental study was designed based on a three component system: the oil phase X_1 (a mixture of Labrafil®/Capmul®, 2:1, w/w), the surfactant X_2 (a mixture of Cremophor®/Tween® 80, 1:1, w/w) and the co-surfactant X_3 (Transcutol®). The total concentration of the three components summed to 100%. The drug content is kept constant 4 mg/g of the prepared SNEDDS. Based on the previous results obtained from phase diagram, the range of each component was selected as follows: X_1 (10–50%), X_2 (30–60%) and X_3 (20–50%). The absorbance of diluted SNEDDS (Y_1), mean droplet size (Y_2) and cumulative amount of drug released after 15 min (Y_3) were used as the responses (dependent variables). The responses of all model formulations were treated by Design-Expert® software (version 7; Stat-Ease, Inc., Minneapolis, MN). Suitable models for mixture designs consisting of three components include linear, quadratic and special cubic models. The best fitting mathematical model was selected based on the comparisons of several statistical parameters including the standard deviation (SD), the multiple correlation coefficient (R^2), adjusted multiple correlation coefficient (adjusted R^2) and the predicted residual sum of square (PRESS), proved by Design-Expert software. Among them, PRESS indicates how well the model fits the data, and for the chosen model it should be small relative to the other models under consideration (Huang et al., 2004).