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Study of cosurfactant effect on nanoemulsifying area and development of lercanidipine loaded (SNEDDS) self nanoemulsifying drug delivery system

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ABSTRACT

The present study deals with the development and characterization of self-nanoemulsifying drug delivery system (SNEDDS) to improve the oral bioavailability of poorly soluble third generation calcium channel blocker lercanidipine (LER). Solubility of the LER was estimated in various oils, cosurfactants and surfactants which were grouped into two different combinations to construct pseudoternary phase diagrams. Various thermodynamic stability and dispersibility tests were performed on the formulations from phase diagram. After constructing phase diagram of two different combinations NL-I and NL-II, the effect of cosurfactants on the nanoemulsifying area was studied and the effect of number and length of hydrophobic alkyl chains of cosurfactant in its emulsification capacity was proved. Percentage transmittance, emulsification time, viscosity and droplet size analysis were used to characterize optimized formulations. The optimized formulation composed of Cremophor EL (45% wt/wt), (13.5% wt/wt) Caproyl 90 with (1.5% wt/wt) Transcutol® HP as per limits of inactive ingredients guidelines of FDA and Maisine oil (10% wt/wt). The mean droplet size in selected nanocarrier system was 20.01 nm. The *in vitro* dissolution profile of LER SNEDDS was found significant in comparison to the marketed LER (Zanidip) tablet and pure drug in pH 1.2, 4.5 and 6.8 buffers. Empty hard gelatin capsule shells were filled using Pfizer's Licap technology and charged on stability conditions of 30 °C/65% RH, 40 °C/65%RH and 50 °C/75% in glass bottles where no significant degradation ($p > 0.05$) was observed in 3 months. The results indicate that SNEDDS of LER, owing to nanosized, has potential to enhance the absorption of drug.

1. Introduction

Lercanidipine is chemically, 2-[(3,3diphenylpropyl) methylamine]-1,1-dimethylethylmethyl 1, 4-dihydro-2,6-dimethyl-4-(3-nitrophenyl)-3,5 pyridinedicarboxylic ester (Fig. 1). It is a new third generation amphiphilic drug which belongs to the well-known pharmacological active compound series classified as 1,4-dihydropyridine calcium channel blockers [1,2].

This drug is used in hypertension treatments, based on its selectivity and specificity on the smooth vascular cells [3]. Lercanidipine is a third-generation dihydropyridine calcium channel antagonist, which blocks calcium entry into L-type calcium channels present in smooth muscle cells, thereby, causing peripheral vasodialation and a reduction in blood pressure [4]. After absorption, oral lercanidipine undergoes extensive first-pass metabolism, with approximately equivalent amounts of an oral dose eliminated in the urine and the faeces as metabolites therefore generating mainly inactive metabolites [4]. This molecule corresponds to a new molecular design in which its liposolubility has been increased to obtain a long action [5]. It is an amphypathic drug which is transported quickly across the cellular barrier, arriving inside to both hydrophilic and hydrophobic sites in spite of its highest solubility in the lipophilic bilayer [5]. Literature suggests single dose of 10 and 20 mg of LER has mean half-lives of 2.8 and 4.4 h in humans, respectively [6]. After oral administration, LER is completely and erratically absorbed from the gastrointestinal tract [6]. However, absolute bioavailability is reduced to approximately 10% because of extensive first pass metabolism to inactive metabolites as undergone by other drugs under the class dihydropyridines of calcium channel blockers [7]. These pharmacokinetic parameters make LER a suitable candidate for development of SNEDDS formulation to enhance oral bioavailability, avoiding first pass metabolism by getting absorbed through lymphatic pathway.

Lipid based formulations represents a unique solution to delivery of poorly soluble compounds. A lipid dosage form typically consists of one or more drugs dissolved in a blend of lipophilic excipients such as triglycerides, partial glycerides, surfactants or co-surfactants [8]. Among the lipid-based systems, the self-microemulsifying drug delivery system (SMEDDS) is a promising technology to improve the rate and extent of absorption of poorly

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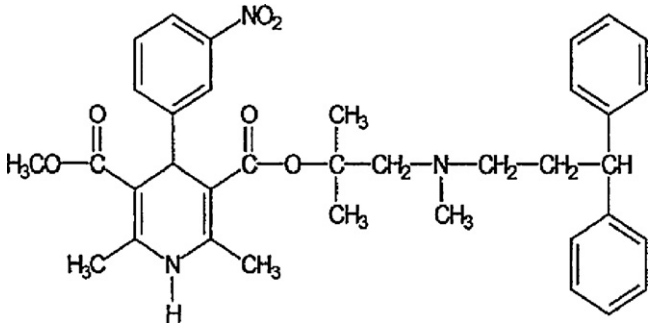

Fig. 1. Chemical structure of lercanidipine.

water-soluble drugs [9]. Self-emulsifying drug delivery systems (SEDDS) are isotropic mixtures of drug, lipids and surfactants, usually with one or more hydrophilic co-solvents or co-emulsifiers [10]. Hydrophobic drugs can be dissolved in these systems, enabling them to be administered as a unit dosage form for per-oral administration [11]. When such a system is released in the lumen of the gastrointestinal tract, it disperses to form a fine emulsion (micro/nano) with the aid of GI fluid [11]. This leads to in situ solubilization of drug that can subsequently be absorbed by lymphatic pathways, by passing the hepatic first-pass effect [11].

Extensive survey of literature and patent databases did not reveal any SNEDDS formulation developed of LER for improving bioavailability. The present investigation was aimed at developing SNEDDS for the delivery of LER. SNEDDS of LER with globule size <100 nm were successfully developed as also shown by images of TEM. Characterization of optimized formulation, *in vitro* evaluation and stability studies of LER formulation was performed which are presented in this investigation. The oral formulations of LER are rapidly metabolized and incompletely absorbed, limiting its use in hypertension. This enhances need to develop a formulation which offers quick dissolution and complete absorption in order to yield improvement in bioavailability and therapeutic efficacy of LER.

Thus, the objectives of the present study were to develop and characterize an optimal self emulsifying drug delivery system formulation of lercanidipine to avoid first pass metabolism of drug thus enhancing oral bioavailability and to study the effect of cosurfactant combinations on nanoemulsifying area in phase diagram.

2. Material and methods

2.1. Materials

Lercanidipine was received as a gift sample from Glenmark Pharmaceuticals Limited, batch number (A22026013) (Mumbai) and certified to contain (99.81% purity). Excipients were chosen based on their functionality, widespread commercial use, solubility with drug and biological properties. Compatibility with various Surfactants, Cosurfactants and Oils were examined. All excipients were US Pharmacopeia/National Formulary grade. The following materials were donated by Gattefosse (Mumbai, India) and were used as received: Labrafac CM10 (C8–C10 polyglycolized glycerides), Labrasol (Caprylo Caproyl macrogolglycerides), Maisine 35-1 (glyceryl monolinoleate), Lauroglycol 90 (propylene glycol monolaurate), Labrafil M1944 CS (Oleoyl macrogoglyceride), Labrafac PG (propylene glycol caprylate/caprate), Transcutol® HP (Diethylene glycol monoethyl ether), Pluro oleique (Polyglyceryl oleate), Caproyl 90 (Propylene glycol monocaprylate) and Capmul (Glyceryl mono or dicaprate). Cremophor RH 40 (Polyoxyl 40 hydrogenated castor oil) and Cremophor EL (polyethoxylated castor oil) were obtained from BASF (Mumbai). Tween 80 (polyoxyethylene sorbitan monooleate) and PEG (Polyethylene glycol) 400 were bought from Merck (Mumbai, India). LR grade castor oil and isopropyl myristate were also used. Deionized water was obtained in the laboratory, using ionic interchanged columns Milli-Q (Millipore). HPLC grade methanol from (Fisher Scientific, Mumbai) was used as received for analysis of bulk drug and formulation on HPLC. Empty hard gelatin capsule shells (size 2) were filled using Pfizer's Licap technology.

2.2. Screening of excipients

The solubility of lercanidipine was ascertained in oils, surfactants, and cosurfactants. An excess amount of LER was added in 2 mL of the selected lipophile in stopperred vials and mixed with the help of vortex mixer (Nirmal International, Delhi, India). These vials were then kept at $25 \pm 1\,^{\circ}C$ in an isothermal shaker (Nirmal International, Delhi, India) for 72 h. The resulting samples were centrifuged at 3000 rpm for 15 min (REMI International, Mumbai, India). The supernatant was filtered through a 0.22 μm filter. The concentration of LER in the supernatant was then quantified by using in house validated HPLC method with UV detector at 240 nm.

2.3. HPLC analysis of LER

The solubility of LER in various excipients was determined by a validated in-house HPLC method. The HPLC apparatus consisted of Agilent HPLC (1120 series) binary pump system and UV detector (Switzerland) equipped with a column compartment with temperature control and an on-line degasser. Data collection and integration was accomplished using EZChrom Elite software. A C18 reverse phase column [(Agilent TC C18 (2), 250 mm × 4.6 mm), particle size 5 μm, Agilent, Switzerland] equipped with a guard column of same packing material was used for the study. Mobile phase consisted of Methanol/Millipore Water at (90:10 v/v) at 1.2 mL/min flow rate, detection at 240 nm with retention time at 5.53 min (Fig. 2). The same method was used in stability studies of formulation kept for 3 months by carrying out assay of drug content in formulation.

2.4. Excipient compatibility studies

On the basis of solubility studies it was found that lercanidipine has high solubility in surfactants (Cremophor EL, Labrasol), cosurfactants (Caproyl 90, Lauroglycol 90 and Transcutol) and in oils (Maisine oil, Labrafil M1944CS). Thermal and non thermal techniques were used to detect any interaction between drug and selected excipients. Samples from stopperred vials containing excess drug loaded excipients were subjected to Differential Scanning Calorimetry (DSC) Pyris 6 DSC, Perkin Elmer (Software pyris series) and Fourier transform infrared spectroscopy (FTIR) (Shimadzu, Japan) and thermograms were obtained.

2.5. Phase diagram studies

Based on solubility studies, one combination (NL-I) comprises of Cremophor EL as surfactant, Capryol 90 with Transcutol® HP (90:10 wt/wt) as cosurfactant and Maisine as the oil phase. Other combination (NL-II) comprises of Labrafil M1944CS, Labrasol and Lauroglycol 90 as the oil, surfactant and cosurfactant respectively. Double distilled water was used as the aqueous phase. The pseudo-ternary phase diagrams were constructed by titration of homogenous liquid mixtures of oil, surfactant and cosurfactant with water at room temperature. Surfactant and cosurfactant were mixed (Smix) in different volume ratios (1:1, 1:2, 1:3, 2:1, 3:1 and 4:1). The ratios were chosen such as by increasing concentration of surfactant with respect to cosurfactant and vice versa. For every phase diagram, oil and specific Smix ratio was mixed in volume