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Cationic solid self micro emulsifying drug delivery system (SSMED) of losartan: Formulation development, characterization and *in vivo* evaluation

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ABSTRACT

The objective of the study was to develop solid self micro emulsifying drug delivery system (SSMED) for enhancement of oral bioavailability of losartan (LOS). Solubility of LOS in various vehicles was determined. Micro emulsion region was identified by constructing phase diagram containing surfactant: co-surfactant mixture (1:1 and 2:1), oil and water. Formulations were initially checked for droplet size upon addition to water. The formulations, which resulted in <200 nm size were further evaluated for self micro emulsification time, phase separation, effect of dilution and pH on droplet size, freeze-thaw stability. The optimized formulation (SMEDDS-C2) was positively charged and contained Capmul MCM 24%; Cremophor EL 37.5%; Transcutol P 37.5% and 1% stearyl amine and had an average particle size 142.51 ± 3.46 nm, zeta potential of +16.66 ± 0.46 mV. The SSMEDs were prepared by adsorption on 4 different carriers. Based on micromeritics, SSMED containing neusilin US2 (SSMED-N) was selected, characterized by DSC, XRD, SEM studies and *in vitro* dissolution. The *in vitro* release from liquid SMEDDS and SSMED-N was found to be significantly higher than LOS. The relative bioavailability of cationic SSMED-N in wistar rats was 2.82 times more than a drug suspension and stable for 3 months at room temperature (RT).

1. Introduction

Poor aqueous solubility and low dissolution rate of drugs in the gastro-intestinal fluids frequently cause reduced bioavailability. Particularly for biopharmaceutical classification system (BCS) class II substances, the bioavailability may be enhanced by increasing the solubility and dissolution rate of the drug in the gastro-intestinal fluids [1]. To overcome this solubility and dissolution rate problems many formulation strategies, such as micronization, solid dispersions [2], complexation with cyclodextrin [3], nano suspensions [4] and self micro or nano emulsified drug delivery systems [5–8] were studied.

Currently, much importance is given for lipid delivery formulations. Among them, self-emulsifying drug delivery systems (SEDDS) and self-micro emulsifying drug delivery systems (SMEDDS) are important to improve the oral bioavailability of poorly water-soluble drugs [9, 10]. These delivery systems promote the lymphatic transport of drugs. SMEDDS are defined as isotropic multi component drug delivery systems composed of oil, surfactant and co-surfactant/co-solvent, which form micro emulsion with droplet size of less than 200 nm in the presence of water [11–13]. Incorporated drugs are in dissolved state rather than in precipitated (amorphous or crystalline) state, there by promoting the release process after oral administration. Cationic emulsions are reported to increase the oral bioavailability. The positive charge on emulsion globules favor the uptake of delivery system by negatively charged biological membranes. The benefits of the positively charged particles include: prolonging the blood circulation time of drugs, enhancing the possibility of its interaction with target cells, good protein adsorption, higher phagocytic uptake and changing the pharmaceutical properties of micro systems which altogether leads to more drug absorption [14]. Cytotoxicity was also reported with cationic polymers in some studies [15]. In many studies stearyl amine was used as charge inducer to improve the oral bioavailability of drugs. Some of them include nanoemulsions [16], transdermal delivery systems [17] and solid lipid nanoparticles [18]. Conventional SMEDDS are widely studied for enhancement of oral

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absorption of poorly-soluble drugs. High concentration of surfactant in SMEDDS formulations can cause GI side-effects [19, 20]. SMEDDS generally produce a stable o/w type of emulsion in which the drug is present in solubilized form, thereby increasing dissolution and bioavailability. However, these delivery systems have some limitations such as interaction between formulation and capsule shell [21]. To overcome the problems mentioned above solid self-micro emulsifying drug delivery systems (SSMEDs) have come into attention which possessed combined advantages of liquid self-micro emulsifying drug delivery systems (L-SMEDDS) and solid dosage forms i.e., solubility, bioavailability enhancement and high stability along with various solid dosage form options [22–25].

Various techniques are known for converting L-SMEDDS to SSMED, which include a) adsorption onto solid carriers, b) melt granulation melt extrusion/extrusion spheronization and c) spray drying. But adsorption process is simple and involves addition of the liquid formulation to solid carriers by mixing in a blender [26]. In recent years low density porous carriers with large surface area, composed of porous silica (Sylysia) as well as magnesium alumino metasilicate (Neusilin) were used in order to improve bioavailability of poorly water soluble drugs [27, 28].

Losartan (LOS) is (2-butyl-4-chloro-1-{[2′-(1H-tetrazol-5-yl) biphenyl-4-yl]methyl}-1H-imidazol-5-yl)methanol having 4.2 log P value and belongs to BCS class II. LOS is angiotensin II receptor antagonist and used for the treatment of hypertension. LOS has low aqueous solubility and high first pass metabolism. Oral bioavailability of the LOS is 25–30% and reported biological half-life is 4 h. Hence, it is necessary to increase the dissolution and oral bioavailability of LOS [29, 30]. LOS is available as normal tablets and film coated tablets in the market which do not play any special role in improvement of oral bioavailability, and till now there are no reports on SMEDDS of LOS.

The objective of this study was to prepare cationic SSMEDs, as potential drug delivery system for LOS. Pseudo ternary phase diagrams were plotted to identify the micro emulsion region and the selected compositions from this region were characterized for self micro emulsification time, phase separation, effect of dilution and pH on droplet size and freeze-thaw stability. Optimized L-SMEDDS was further adsorbed onto different solid carriers to get SSMED. Based on micromeritics of the SSMEDs, one of them was chosen as optimized SSMED. Further, the optimized cationic SSMED was characterized and evaluated for the improvement in oral bioavailability in wistar rats.

2. Materials and methods

2.1. Materials

Losartan potassium was a gift sample from Aurobindo Pharma, Hyderabad. Labrafac Lipophile WL1349, Labrasol, Lauroglycol 90, Labrafil M1944 CS, Labrafil M2125 CS and Transcutol P were gift samples from Gattefosse, USA. Capmul MCM was a gift sample from ABITEC Corporation, USA. Cremophore EL was gifted by BASF, India. Oleic acid, Tween 80, PEG 400 and Mannitol were purchased from Merck, India. Neusilin US2, Sylysia 350 and Sylysia 770 were gifted by Fuji chemicals, Japan. Stearyl amine was purchased from Sigma Aldrich, Mumbai. Hard gelatin capsules were gifted by ACG capsules Pvt Ltd., Mumbai. All other chemicals used were of analytical grade and solvents were of HPLC grade.

2.2. Methods

2.2.1. Conversion of losartan potassium to losartan base

Aqueous solution of losartan potassium was titrated with 0.1 M HCl, the formed precipitate was separated by filtration and repeatedly washed until the pH of washings was same as that of double distilled water. The purity of LOS was determined by melting point (MP) and confirmed by using differential scanning calorimetry (DSC).

2.2.2. Solubility studies

The solubility of LOS in various vehicles was measured [31]. Here, different oils, surfactants and co-surfactants were used (Table 1). Exactly, one gram of selected vehicle was added to each capped vial containing an excess of LOS. After wards, the mixture was heated for 2 min at 40 °C in a water bath and vortexed. Then these mixtures were kept on a bench top gyratory shaker (GFL, Germany) at 180 rpm for 24 h at RT. After 24 h, the mixture was taken in an eppendorf tube and centrifuged at 4000 rpm for 10 min. The supernatant was filtered through a 0.45 μm membrane filter (Whatman, USA) and diluted with methanol. LOS concentration was quantified by HPLC.

2.2.3. Construction of pseudo ternary phase diagram

On the basis of solubility and emulsification studies – oil (Capmul MCM), surfactant (Cremophor EL, Tween 80) and co-surfactant (Transcutol P) were selected. To determine micro-emulsion zone, pseudo ternary phase diagrams were constructed using water titration method [20]. Mixture containing different ratios (1:1, 2:1) of surfactant and co-surfactant (S_{mix}) were prepared. The oil and S_{mix} were taken in ratios of 1:9, 2:8, 3:7, 4:6, 5:5, 6:4, 7:3, 8:2 and 9:1 with a total quantity of 1 g. The mixtures were vortexed and titrated with water using a micro syringe under gentle agitation and observed visually for any turbidity. Percent of components was figured out by constructing a pseudoternary phase diagram using Triplot software v 4.1.2 (Todd A. Thompson, USA).

2.2.4. Preparation of L-SMEDDS

Accurately weighed amount of LOS (10 mg) was placed in a glass vial containing Capmul MCM (24%), Cremophor EL (37.5%) and Transcutol P (37.5%) as oil, surfactant and co-surfactant (S_{mix}) respectively. The contents were vortexed for 20 min and heated at 37 °C so as to obtain a homogeneous isotropic mixture. Then, 1% of stearyl amine (charge inducer) was added and vortexed for 5 min. The prepared L-SMEDDS formulation was stored at room temperature until used [5].

2.2.5. Characterization of L-SMEDDS

2.2.5.1. Assessment of self-micro emulsification time, phase separation and freeze – thaw stability. Self micro emulsifying properties of L-SMEDDS formulations were performed by visual assessment. The time taken for emulsion (until a homogenous system was obtained)

Table 1
Solubility of losartan in different vehicles (mean ± SD, n = 3).

Vehicles	Solubility (mg/g)
Capmul MCM	6.48 ± 1.01
Lauroglycol 90	2.10 ± 1.42
Labrafac WL1349	0.88 ± 0.28
Castor oil	0.54 ± 0.12
Oleic acid	0.65 ± 0.33
Labrasol	13.49 ± 2.27
Tween 80	19.66 ± 1.35
Cremophore EL	28.10 ± 2.14
Transcutol P	58.81 ± 3.83
PEG 400	17.13 ± 0.32
Labrafil 1944CS	0.55 ± 0.14
Labrafil 2125CS	5.71 ± 2.73