ORIGINAL ARTICLE

Preparation and Evaluation of Self-micro Emulsifying Drug Delivery Systems of Lercanidipine HCl using Medium and Short Chain Glycerides: A Comparative Study

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Abstract

Aims: The aim of this study was to formulate a self-microemulsifying drug delivery system (SMEDDS) of Lercanidipine HCl (LCH) using medium chain (MC) and short chain (SC) glycerides as oil phase and to compare the dissolution efficiency of both formulations. **Materials and Methods:** Different oils and surfactants containing MC and SC fatty acid as basic molecule were screened using quantitative solubility study and constructing pseudoternary phase diagrams. Cosolvents were used as cosurfactants. The preconcentrates were tested for a self-microemulsifying time, % transmittance, cloud point, globule size, zeta potential, and *in-vitro* drug release. Selected formulations were compared by calculating dissolution efficiencies in different pH media. **Results:** Capmul MCM, Cremophor® RH 40, and polyethylene glycol 400 were chosen as oil, surfactant, and cosurfactant, respectively, for MC glyceride and triacetin and Tween 80 were selected as oil and surfactant for SC triglyceride category, respectively. All the formulations spontaneously resulted into transparent microemulsion with globule sizes range from 50 to 90 nm for MC-SMEDDS and 200-317 nm for SC-SMEDDS. The formed microemulsions were stable as shown by zeta potential and cloud point determination. However, *in-vitro* drug release in 0.1 N HCl showed quite a similar dissolution of all the formulation batches, a study in the different pH media showed that LCH being weak base, possess pH dependent solubility. **Conclusions:** The MC-SMEDDS were able to resist the effect of pH on dissolution to some extent as compared to pure untreated LCH and simple mixture of oil and surfactant. This piece of research strongly established the need for biorelevant dissolution interphase to differentiate between the formulations.

Key words: Capmul MCM, Lercanidipine HCl, self-microemulsifying drug delivery system, triacetin

INTRODUCTION

Lercanidipine HCl (LCH) is a highly lipophilic calcium channel blocker used in the treatment of hypertension. The poor water solubility and high log P value make its dissolution difficult resulting in poor systemic concentrations.[1,2] Moreover, the drug undergoes first pass effect and hence oral bioavailability is reported to be only 10%.[3] Therefore, the first step toward improving its bioavailability can be an improvement in dissolution.

During the last 15 years, numerous dissolution enhancement had been evolved as a useful alternative for poorly water-soluble drugs. However, an efficient dissolution enhancement technique is one that not only improve dissolution *in-vitro* but also impart dissolution stability *in-vivo,* i.e. not affected by changes of pH, presence of bile salts and phospholipids and surface tension in the gastric environment. Since years, emulsion had remain proven methodology for improving the dissolution of poorly water-soluble drugs due to the high efficiency of the oil phase to solubilize the lipophilic drug.

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To name a few, oily solution, emulsion, microemulsion, nanoemulsion, self-emulsifying drug delivery systems (SEDDS), self-microemulsifying drug delivery system (SMEDDS), and solid SEDDS (solid dispersion) are the positive examples of techniques for dissolution enhancement.[4] Lipophilic drugs are easily solubilized in oils and can be presented directly in solution form, avoiding the dissolution step to facilitate the rapid absorption and thus bioavailability.[5] A variety of mechanisms is believed to be involved in the improvement of the bioavailability of hydrophobic drugs by lipid based formulations. Inhibition of P-glycoprotein-mediated drug efflux,[6] promotion of lymphatic transport, which delivers the drug directly to the systemic circulation while avoiding hepatic first-pass metabolism[7-9] and increasing gastrointestinal (GI) membrane permeability[10] are some of the important mechanisms of bioavailability enhancement. In addition to these mechanisms, an important advantage of SEDDS is the availability of prodigious surface area of the oil globules. Moreover, SEDDS is easy to formulate and can be easily administered in the form of soft gelatin or hard gelatin capsules. SEDDS has become favorite formulation strategy for poorly water-soluble and poorly bioavailable drugs not only in research fraternity[11-21] but is also accepted by pharmaceutical industries at large. To name a few, Sandimmune® and Sandimmune Neoral® (cyclosporine A), Norvir® (ritonavir), and Fortovase® (saquinavir) are successful examples of marketed SEDDS.

There has been extensive research on the materials used for preparing SEDDS. In general, the lipid phase used to prepare SEDDS/SMEDDS is divided into three categories depending on the chain length of the fatty acids, i.e., long chain (LC) triglycerides, medium chain (MC) triglycerides, and short chain triglycerides (SCT). Recently, MC mixed glycerides have evolved to be popular excipients, having the even greater solvent capacity, superior ability to promote emulsification, and very less or no susceptibility to oxidation.[22] Several studies have been published reporting MC glycerides for developing SEDDS of a wide variety of drugs.[23-26] According to these studies, being small molecular volume oil phase, medium chain glycerides showed the high solvent capacity and excellent miscibility with other surfactants and co-surfactants and enhanced the permeability and bioavailability of candidate drugs. While SCT, such as Triacetin, has not been widely explored for preparing SMEDDS.

Hence, the main objective for the present part of the study was to develop and evaluate SEDDSs using lipids with medium and SC fatty acid, for dissolution enhancement of LCH. The oil phase for SEDDS was categorized as MC mix glycerides (MCG) and SCT. Therefore finally, two formulations, i.e., MC-SMEDDS and SC-SMEDDS were prepared, characterized and compared to derive the optimized formulation.

MATERIALS AND METHODS

LCH was received as a generous gift from Torrent Research Center, Ahmedabad, India. Capmul PG-12 EP/NF (propylene glycol monolaurate), Captex-355 EP/NF (glycerol tricaprylate/caprate), Capmul MCM EP (glycerol monocaprylocaprate) were obtained as gratis samples from Indchem International C/O ABITEC Corporation, USA. Labrafac Lipophile WL 1349 (Triglycerides MC EP), Gelucire® 44/14 (Lauroyl macrogol-32 glycerides EP), Labrafil® M2130CS (Lauroyl macrogol-6 glycerides EP), Labrasol® (Caprylocaproyl macrogol-8 glycerides EP), Capryol™ 90 (propylene glycol monocaprylate [Type II] NF), Lauroglycol™ 90 (propylene glycol monolaurate [Type II] EP/NF), and Transcutol® P (purified diethylene glycol monoethyl ether EP/NF) were received as generous gift from Gattefosse India. Cremophor® RH 40 (Polyoxyl 40 Hydrogenated Castor Oil) and Cremophor® EL (Polyoxyl 35 hydrogenated castor oil) were obtained from BASF India. Food grade coconut oil was purchased from local market. Tween 20 (polyethylene glycol [PEG] sorbitan monolaurate), Tween 80 (polyoxyethylene [20] sorbitan monooleate), and PEG 400 were purchased from Otto Chemie Pvt. Ltd. (Mumbai, India). Triacetin was obtained from Chemdyes Corporation, Ahmedabad, India.

Solubility study

Saturation solubility of LCH was checked in all the liquid excipients containing MC lipids by shake flask method.[27] An excess amount of drug was added in 2 ml of all the liquid excipients and heated at 40°-45°C on a water bath for 10 min. The samples were stirred for 24 h on a rotary shaker and centrifuged at 2000 rpm for 15 min. The heterogeneous systems were allowed to reach equilibrium for up to 10 h. Supernatants were filtered through Whatman filter paper (0.45 µm) and analyzed for LCH at 364.5 nm using ultraviolet spectrophotometer (Shimadzu, Japan) keeping the pure excipient as the reference standard.

The SCT 1, 2, 3-triacetoxypropane which is more generally known as triacetin and glycerinetriacetate was tested for solubility of LCH as described earlier. There were no surfactants and cosurfactants found to have SC lipids and therefore the non-ionic surfactants like Tween(s) and Cremophor(s) and other cosolvents like PEG and Transcutol P were chosen for the study.

Pseudoternary phase diagrams

Phase diagrams were drawn to identify the blends of oil-surfactant-cosurfactant that gives microemulsion employing water titration method. Capmul MCM and Capmul PG 12 were selected as oil phase for MC glycerides category and

analyzed with different combinations of surfactants and cosurfactants as shown in Table 1. Triacetin (SCT) was also tested with nonionic surfactants and cosolvents for drawing the phase diagrams. The oil phase was mixed with different combinations of surfactants and co-surfactants in ratio of 0:10, 1:9, 2:8, 3:7, 4:6, 5:5, 6:4, 7:3, 8:2, 9:1 and 10:0. The water was added drop wise to the blends of oil-surfactant-co-surfactant and the points at which the mixture transits from clear-turbid-clear were noted and was plotted on the ternary/pseudo-ternary phase diagrams using ProSim software. The combination showing highest % isotropic region and maximum fully dilutable lines and not showing any signs of drug precipitation were selected for further study.

Preparation of preconcentrates

From the results of the pseudoternary phase diagrams, the only composition giving fully dilutable lines were taken for the formulation development. LCH (10 mg) was dissolved in the oil phase, i.e., Capmul MCM or triacetin. The mixture of surfactant: Cosurfactant, i.e., Cremophor RH 40: PEG 400 (4:1) was added to the oil phase (Capmul MCM) with continuous stirring. While tween 80 was added to triacetin. The mixture was allowed to homogenize at 40°C for 24 h and was stored in stoppered glass vial until further evaluation. The total amount the mixture was kept constant at 0.48 ml [Table 2] to be filled into size 1 hard gelatin capsules. To facilitate the comparison between the MC-SMEDDS and SC-SMEDDS and to explain the role of the oil phase in dissolution enhancement, a simple mixture of Capmul MCM (40%) and Tween 80 (60%) was prepared and denoted as MC-4:6.

Characterization of SMEDDS

The preconcentrates (0.1 ml) of MC-SMEDDS and SC-SMEDDS were diluted with 0.1 N HCl to produce 100 ml of the microemulsion. Self-microemulsification time and percentage transmittance, cloud points, globule size, and zeta potential were determined.

Self-microemulsification time and % transmittance

The preconcentrate and 0.1N HCl were blended under the action of propeller stirrer at a constant speed of 50 rpm at 37±5°C temperature. Microemulsification times were measured visually observing the mixture and

Table 1: Result of quantitative solubility study

Oils	Solubility of LCH in mg/ml ± S.D	Surfactants	Solubility of LCH in mg/ml ± S.D	Co-surfactants and co-solvents	Solubility of LCH in mg/ml ± S.D
Capmul MCM	60.83 ± 1.25	Gelucire® 44/14#	102 ± 2.98	Capryol™ 90	40 ± 0.78
Capmul PG-12	52.48 ± 0.65	Labrafil® M2130CS#	41.65 ± 1.75	Lauroglycol™ 90	45 ± 0.38
Captex-355	11 ± 0.84	Labrasol®#	89.37 ± 0.34	Polyethylene glycol 400	90 ± 0.97
Labrafac Lipophile	5 ± 0.75	Cremophor RH 40*	150.62 ± 0.61	Transcutol P	470 ± 0.74
Coconut oil	3.87 ± 0.96	Cremophor EL*	56.53 ± 0.68	-	
Triacetin (SCT)	109 ± 3.35	Tween 80*	500 ± 0.99		
		Tween 20*	13.1 ± 0.39		

#Lipidic excipient, *Non-ionic surfactant. SCT: Short chain triglycerides, LCH: Lercanidipine HCl

Table 2: Preparation scheme for SMEDDS

Batch	% Quantity		
	Oil	surfactant	Co-surfactant
For MC-SMEDDS	Capmul MCM	Cremophor® RH 40	PEG 400
M1	10	72	18
M2	20	64	16
M3	30	56	14
M4	40	48	12
For SC-SMEDDS	Triacetin	Tween 80	
S1	10	90	-
S2	20	80	-
S3	30	70	-
S4	40	60	-

SMEDDS: Self-microemulsifying drug delivery system, SC: Short chain, MC: Medium chain, PEG 400: Polyethylene glycol 400

percent transmittance were measured at 650 nm in UV spectrophotometer.[28]

Cloud point determination

The cloud points were determined for the resultant microemulsions to see the effect of temperature on stability. The samples were kept in a water bath which was initially maintained at a temperature of 25°C with a gradual increase in temperature at the rate of 5°C/min and the corresponding cloud point temperatures were noted at the first sign of turbidity by visual observation.[1]

Globule size evaluation

The globule size was determined by dynamic light scattering technique using Zetasizer (Zetasizer Nano ZS, Malvern Instruments, UK) employing He–Ne red laser, 4.0 mW, 632.9 nm, temperature of 25°C, refractive index of 1.45. All measurements were done using disposable polystyrene cuvettes (Malvern Instruments, UK). The mean globule size and polydispersity index were recorded for every sample.[1]

Zeta potential measurement

The same samples as prepared for the globule size evaluation were used for zeta potential measurement. The surface charge was measured by Zetasizer (Zetasizer Nano ZS, Malvern Instruments, UK). The refractive index and viscosity of the dispersant were kept as 1.45 and 1.1, respectively.

In-vitro drug release study

The preconcentrates of MC-SMEDDS and SC-SMEDDS (0.48 ml containing 10 mg drug) were filled into capsule size 1 with the help of micropipette. An *in-vitro* dissolution study was conducted in US Pharmacopoeia XXIV Type II paddle apparatus with sinkers. 0.1 N HCl was used as dissolution medium. The rotation speed of paddles was kept at 75 rpm. The aliquots (5 ml) were withdrawn at 5, 10, 15, 30, 45, and 60 min and, the samples were analyzed by UV spectrometry at 364.5 nm. The standard curve was plotted in the dissolution medium, i.e. 0.1 N HCl (Absorbance = 0.0101*Concentration + 0.015).

Comparison between the medium and Short Chain SMEDDS

For comparison between the formulations, dissolution efficiencies were calculated as explained by Khan and Rhodes.[29] It is defined as the area under the dissolution curve up to a certain time *t*, expressed as a percentage of the area of the rectangle described by 100% dissolution in the same time. It can be calculated using following formula.

$$D.E.=\frac{\int_0^t y \times dt}{y_{100} \times t} \times 100\ \%$$

Where, *y* is the drug percent dissolved at time *t*.

The areas under the curve were calculated using trapezoidal method. The selected formulations were studied for dissolution efficiency in three different media with a pH range representing normally encountered changes in gastric environment, *viz*., 0.1 N HCl (pH 1.2), pH 5 and 6.5 acetate buffer. Being the weak base, LCH is having pH dependent solubility, therefore, this study was carried out to check the robustness of the formulation to withstand the change in pH and to keep the drug in dissolved state.

RESULTS AND DISCUSSION

Solubility study

The results of quantitative solubility study conducted in duplicate are shown in Table 1. Solubility study showed Capmul MCM and Capmul PG 12 among MCG with high LCH solubility and hence were selected for plotting phase diagrams. In the case of surfactants, Tween 80 and Cremophor® RH 40 showed the highest solubility while Gelucire® 44/14, Labrasol® showed LCH content in decreasing order. Here, Cremophor RH® 40 and Tween 80 are non-ionic surfactants while other two are lipidic excipients containing MC fatty acid. In the case of cosurfactants Transcutol® P and PEG 400 showed high solubility followed by Lauroglycol® 90. Triacetin, the only SCT showing solubility of LCH 109 mg/ml was taken as oil phase for making SC-SMEDDS.

Pseudoternary phase diagrams

The goal of constructing the pseudoternary phase diagrams was to achieve large % isotropic region and maximum fully dilutable oil: (surfactant-co-surfactant) mixture lines. The maximum isotropic region provides a wide choice of combinations of excipients which can help in cost optimization and ultimately benefit to manufacturers. Because any composition of excipients chosen within this region would result in microemulsion. Fully dilutable lines indicate dilution without affecting the microemulsion *in-vitro* and ensure dilution with GI fluids without precipitation and ultimately the biorelevancy. Hence, it indirectly indicates that batch failure rate, due to precipitation, dissolution, and bioavailability, decreases.

Results of phase diagrams are depicted in Table 3 and Figure 1a-k. Transcutol P, as a cosurfactant in all the combination, showed precipitation of the drug on standing, which can be attributed to its high solubilizing capacity and being a cosolvent which on mixing with water gives out LCH due to salting out effect. Hence, it was not considered for further study. Capmul MCM gave either <50% isotropic region or none fully dilutable lines with surfactants with MC fatty acids, i.e., gelucire 44/14 and labrasol (Results not

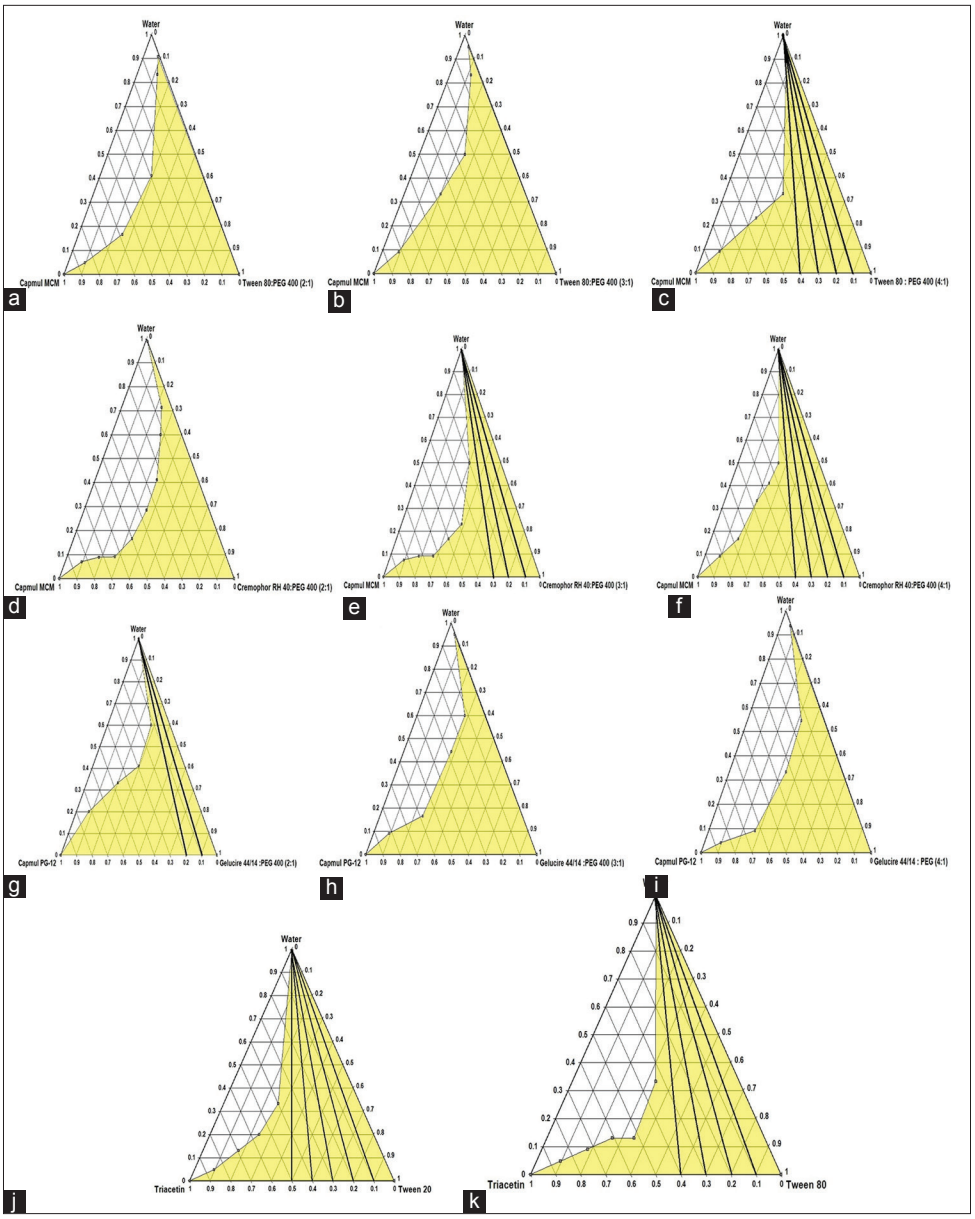

Figure 1: Pseudoternary phase diagrams of combination a-k as indicated in Table 3

Table 3: Result of pseudoternary phase diagrams

Combination	Oil phase	Surfactant: Co-surfactant	Fully dilutable lines	% Isotropic region*
A	Capmul MCM	Tween 80: PEG 400 (2:1)	None	61.41
B	Capmul MCM	Tween 80: PEG 400 (3:1)	None	71.01
C	Capmul MCM	Tween 80: PEG 400 (4:1)	1:9, 2:8, 3:7, 4:6	64.60
D	Capmul MCM	Cremophor RH 40: PEG 400 (2:1)	None	53.05
E	Capmul MCM	Cremophor RH 40: PEG 400 (3:1)	1:9, 2:8, 3:7	56.53
F	Capmul MCM	Cremophor RH 40: PEG 400 (4:1)	1:9, 2:8, 3:7, 4:6	70.20
G	Capmul PG-12	Gelucire 44/14: PEG 400 (2:1)	1:9, 2:8	68.55
H	Capmul PG-12	Gelucire 44/14: PEG 400 (3:1)	None	59.62
I	Capmul PG-12	Gelucire 44/14: PEG 400 (4:1)	None	54.22
J	Triacetin	Tween 20	1:9, 2:8, 3:7, 4:6, 5:5	69.44
K	Triacetin	Tween 80	1:9, 2:8, 3:7, 4:6	60.23

*Calculated using AutoCAD® 2014 software

shown). Moreover, formed microemulsion was not stable for even 12 h. The highest % isotropic region was observed in the case of combination A-C as mentioned in Table 3 containing Capmul MCM as oil and Tween 80 and PEG 400 as surfactant and cosurfactant, respectively. Combination C gave 4 fully dilutable lines with 64% isotropic region. But on standing for 24 h, creaming was seen and hence was not considered for formulation. In contrast to Capmul MCM, combinations containing Capmul PG-12 as oil and Gelucire 44/14 and PEG 400 as surfactant and cosurfactant (2:1), respectively, showed two fully dilutable lines. The high isotropic region was observed but after few hours, precipitation of the drug was observed and hence was dropped from the choice of formulation. Finally, combination F, which showed second highest % isotropic region, 4 fully dilutable lines (1:9, 2:8, 3:7 and 4:6), and the resultant microemulsion was clear without signs of creaming and precipitation of the drug till 24 h was selected for further consideration. Combination F contained Capmul MCM as oil and Cremophor® RH 40 and PEG 400 as surfactant and cosurfactant, respectively, in the ratio of 4:1. While 3:1 ratio (Combination E) also gave 3 fully dilutable lines, but combination F was preferentially chosen so as to incorporate the maximum possible amount of oil (40%) in the formulation.

While titrating the triacetin and different surfactant and cosurfactant mixture with water, it was observed that triacetin was not compatible with cosurfactants such as PEG, and transcutol P. Being fully dispersible in water, the triacetin when mixed with other cosolvents resulted into unstable microemulsion showing rapid creaming and coalescence. While, when mixed with only surfactants such as different grades of Cremophor® and Tween 80, satisfactory microemulsions were formed. Out of which Tween 80 and Tween 20 gave more than 65% isotropic region and 4 and 5 fully dilutable lines respectively (Figure 1j and k). Again Tween 80 provided better microemulsion which was stable even after 24 h. While with tween 20, little creaming was observed after storage. Therefore, triacetin with Tween 80 was selected for preparing SC-SMEDDS.

Preparation of SMEDDS

The prepared formulations as denoted in Table 2 were characterized for different parameters. In addition, MC-4:6 was also studied to facilitate the comparison between medium and SC formulations.

Characterization of SMEDDS

The findings of *in-vitro* characterization of all MC-SMEDDS, SC-SMEDDS, and MC-4:6 batches are shown in Table 4.

Self-microemulsification time and % transmittance

All MC-SMEDDS spontaneously formed microemulsion within 21 s. As the amount of Capmul MCM increased from M1 to M4 there was an increase in the self-microemulsifying time from 15 to 21 s. While the reverse trend was observed in the case of SC-SMEDDS, the self-emulsification time decreased as the amount of triacetin increased. The MC-4:6 took 40 sec to be microemulsified. However, the physical appearance remained transparent in all the batches and percentage transmittance was found to be >90%.

Cloud point determination

The cloud points were found to be more than 60°C, which indicates superior thermal stability of formed microemulsions.

Globule size evaluation

The only parameter which helps differentiate the formulations was globule size. In the case of MC-SMEDDS, globule sizes ranged from 50 to 90 nm, as the amount of Capmul MCM increased the globule size also increased. A similar pattern was also observed with SC-SMEDDS, such that as triacetin increased globule sizes increased from 200 to 317 nm. MC-4:6 resulted into transparent microemulsion with globule size of 116.9 nm. Globule size of the resultant microemulsion plays a pivotal role in enhancement of bioavailability. It is established that the smaller the globule size, the higher the

Table 4: *In-vitro* characterization of MC-SMEDDS and SC-SMEDDS

Batch	Self-micro emulsification time	Cloud point in °C	Globule size in nm (PDI)	Zeta potential (mV)	% Transmittance and phase clarity	% Drug release at 60 min
M1	15 s	75	50 (0.25)	NP	97 transparent	100.45±1.24
M2	20 s	75	62.84 (0.54)	NP	97 transparent	98.89±1.58
M3	21 s	74	75.71 (0.31)	NP	96.86 transparent	99.32±2.58
M4	21 s	75	90.83 (0.28)	−8.88	95.79 transparent	101.02±0.35
MC-4:6	40 s	NA	116.9 (0.44)	−2.25	93 slightly bluish tinge	102.04±0.35
S1	22 s	65	200 (0.47)	NP	98.32 transparent	99.48±2.37
S2	20 s	64	238.3 (0.45)	NP	98.12 transparent	95.20±1.58
S3	15 s	69	260 (0.31)	NP	98.01 transparent	98.79±3.58
S4	15 s	67	317.8 (0.37)	−3.33	97.63 transparent	96.95±1.53

SMEDDS: Self-microemulsifying drug delivery system, SC: Short chain, MC: Medium chain

effective surface area available for dissolution and hence absorption. Many studies have reported enhanced oral absorption due to reduction globule size.[30-32] Hence, the prepared SMEDDS showed complete drug release owing to their very small globule sizes.

Zeta potential measurement

Determining the stability of microemulsions *in-vitro* is of less importance in the case of SMEDDS. However, the charge on tiny globules definitely affects the extent of absorption from the negatively charged mucosal surface.[33] Zeta potential values suggested that microemulsions were stable and less likely to pose any problem in the short span of processing in GI tract (GIT). As the drug is already in dissolved form within the formulation, the onset of absorption will be faster.

In-vitro drug release study

In-vitro drug release in 0.1 N HCl from all the formulations showed more than 95% LCH dissolved at the end of 60 min. The finding suggested that there was no correlation between globule size and drug release, rather batch M4 which contains the highest amount of Capmul MCM and which had the highest globule size among MC formulations showed complete 100% drug release at 60 min. In the case of SC-SMEDDS, batch S3 showed more drug release than batch S2, which inversely proportional to globule size. Even MC-4:6 showed complete drug release after 60 min. These results can be attributed to the pH-dependent solubility of LCH. LCH is a weak base, and as long as it is in the dissolved form in the formulation, it is going to be dissolved completely in acidic environment due to the very fine globule size of the microemulsion. In other words, these findings strongly suggested that the *in-vitro* drug release in just the 0.1 N HCl is not capable enough to conclude the optimized formulation among the formulations under study.

Hence, further dissolution study was carried out in two more pH media which reflected the pH range normally prevalent in GIT. For further study batch M4, S4 and MC-4:6 were selected due to their high content of oil phase so that the role of lipid can be explained effectively.

Comparison between medium and Short Chain SMEDDS

Comparative *in-vitro* drug release profiles in different pH media are shown in Table 5. In the case of batch M4, there was a noticeable change in dissolution efficiency from 91.49 to 84.33 as the pH increased from 1.2 to 6.5. This decline can be explained by the fundamental that Capmul MCM and Cremophor® RH 40 present spontaneous formation of microemulsion but because of easy dispersibility of Capmul MCM and hydrophilicity of Cremophor RH 40 they get solubilized in aqueous environment and due to increase in pH the drug exposed to media is not capable of remaining in the dissolved form and it precipitates out. While in the case of batch S4, there was a drastic change in dissolution efficiency from 87.50 to 76.36. This is due to high miscibility of Triacetin being SC glyceride which gives out drug due to salting out effect. On the other hand, MC-4:6 showed a sharp decline in drug release, which can be attributed to very high hydrophilic nature of both Capmul MCM and Tween 80. Moreover, the absence of cosurfactant make the microemulsion unstable,[34] i.e. globules are not capable of retaining their size and hence not able to hold the drug in changing pH environment and drug gets precipitated out. While SMEDDS formulations, due to stability, were able to dissolve the appreciable amount of LCH. However, at the

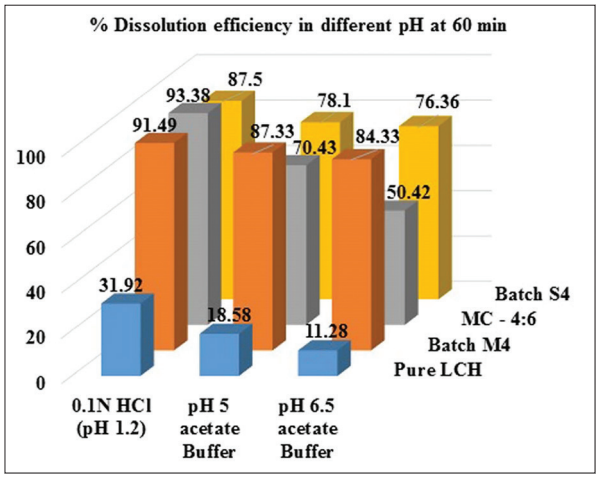

Figure 2: Comparison of dissolution efficiencies between medium and short chain self-microemulsifying drug delivery system

Table 5: Dissolution efficiencies of formulations

Batch No.	% Dissolution efficiency±Standard deviation (*n*=3)					
	0.1 N HCl (pH 1.2)		pH 5 acetate buffer		pH 6.5 acetate buffer	
	5 min	60 min	5 min	60 min	5 min	60 min
Pure LCH	12.72±1.1	31.92±0.44	6.11±0.09	18.58±0.07	5.36±0.03	11.28±0.17
Batch M4	44.57±4.10	91.49±0.35	43.97±0.57	87.33±0.62	41.26±1.53	84.33±3.25
MC-4:6	44.93±4.09	93.38±0.35	26.95±1.38	70.43±0.54	10.56±0.47	50.42±1.98
Batch S4	34.81±2.47	87.50±1.53	33.62±0.98	78.10±0.85	32.13±1.28	76.36±2.48

LCH: Lercanidipine HCl

outset, MC-SMEDDS was found to be superior formulation in dissolving high amounts of LCH in all pH media as can be seen in Figure 2 and also less susceptible to precipitation as compared to SC-SMEDDS. Hence, it can be said that Capmul MCM is better at dissolving LCH than triacetin.

CONCLUSION

SMEDDSs were formulated using medium and SC glycerides in combination with nonionic surfactants and cosurfactants. Prepared SMEDDS were fully dilutable without signs of precipitation. However, MCG provided more efficient SMEDDS than that of the SCT. Both the lipids improve the dissolution of LCH owing to their high solubilizing capacities but the ability to resist the precipitation was higher in case of MC-SMEDDS as compared to SC-SMEDDS. The findings aided in concluding that cosurfactant was essential for maintaining LCH in dissolved form. Formulating SMEDDS requires careful planning of excipient blend which can ensure *in-vitro* as well as *in-vivo* dissolution stability. This study demands an extension of dissolution study with biorelevant media to check the effect of various bile salts and phospholipids on dissolution behavior of SMEDDS. Of course, the *in-vivo* bioavailability study will establish the concrete *in vitro–in vivo* correlation for the successful development of formulation into marketed product.

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