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FORMULATION AND EVALUATION OF SELF-NANO EMULSIFYING SYSTEM FOR TRANSDERMAL DELIVERY OF LERCANIDIPINE HYDROCHLORIDE: INVITRO AND EX VIVO EVALUATION

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ABSTRACT

The prime objective of this investigation was to develop a self-nanoemulsifying drug delivery system (SNEDDS) of a poorly water-soluble drug i. e. Lercanidipine hydrochloride (LRCH) in order to enhance its solubility, dissolution rate and *ex-vivo* diffusion through transdermal route. Numerous oils, surfactants and co-surfactants were examined. Preliminary studies were carried out for the selection of the proper ingredients of the self-emulsifying system depending on the drug solubility and the emulsification power. Pseudo-ternary phase diagrams were constructed at surfactant/co-surfactant ratios of 1:1, 1:2, 1:3, 2:1 and 3:1 (% v/v) by using aqueous titration method to identify the most effective self-nano emulsification region. 3^2 factorial design was applied to optimize SNEDDS. Oil (X1) and Suractant: cosurfactant ratio (X2) were selected as independent variable whereas globule size, emulsification time (Y2), and drug released at 15 minutes (Y3) were taken as dependent variables. Prepared SNEDDS formulations were evaluated for different parameters like globule size (Y1), emulsification time, zeta potential, poly-dispersibility index, phase separation behaviour and percentage transmission. The optimized formulation LFB-6 was composed of 36.36% Capmul® MCM C8 as an oil, 42.42% Cremophor® RH 40 as a surfactant, and 21.22% Transcutol® P as a cosurfactant. Carbomer 941 was added as a gel matrix forming agent to convert nanoemulsion into nanoemulgel. Nanoemulgel was evaluated for rheological characteristics and imbibed in the transdermal patch to check the *ex- vivo* diffusion through pig abdominal skin by using Franz diffusion cell. The drug

diffusion was found to be 99.24 % after 24 h with permeation flux about 375.48 (μg/cm^2/hr). The results indicated that nanoemulsion based nanoemulgel worked as a promising vehicle for transdermal delivery of LRCH.

Keyword: Self-nano-drug delivery systems, pseudo ternary phase diagram, factorial design, Transdermal drug delivery, nanoemulgel, *ex-vivo* diffusion

1 INTRODUCTION

Self-emulsifying drug delivery system has emerged as potential formulations for solving problems of poorly water-soluble drugs; poor dissolution, low bioavailability and lack of dose proportionality. Self-emulsifying drug delivery system has been categorised as self-micro emulsifying (SMEDDS) and self-nanoemulsifying drug delivery systems (SNEDDS) depending upon the droplet size produced after dispersion. SNEDDS are characterized by high solvent capacity, small Particles **[1, 2]**. SNEDDS are isotropic liquid mixtures of oil, surfactant, co-surfactant and drug that form fine, thermodynamically stable oil-in-water nanoemulsion when introduced into the aqueous medium under gentle agitation **[3]**. Major component of SNEDDS are Oil, surfactant and co-surfactants. The use of surfactants plays an important role to improve the bioavailability of the drugs by activation of various mechanisms like maintaining the drug in solution form by avoiding and/or by improving the drug dissolution **[4]** or increasing intestinal epithelial permeability of drugs **[5]** or increasing tight junction permeability of drugs **[6, 7]**. In the development of a SNEDDS, an important issue is to design an optimized formulation with an appropriate globule size with the minimum number of trials. Statistical experimental design methodologies are powerful, efficient and systematic tools in the design of pharmaceutical dosage forms, allowing the rational study of the influence on formulation and/or processing parameters on the selected responses with a shortening of the experiment **[5, 8, 9]**.

Lercanidipine hydrochloride is chemically described as3-O-[1-[3, 3-diphenylpropyl (methyl) amino]-2methylpropan-2-yl]5-O-methyl2, 6-dimethyl-4-(3nitrophenyl)-1,4-dihydropyridine-3,5-dicarboxylatehydro-chloride. It is a new third generation Calcium antagonist used in the treatment of hypertension. The drug is official in Merck index and Martindale. The single dose of 10-20 mg of LRCH has mean half-lives of 2.8 and 4.4 h in humans **[10]**. After oral administration, LRCH is entirely and unpredictably absorbed from the gastrointestinal tract **[11, 12]**. 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 **[13]**. These pharmacokinetic parameters make LCRH a suitable candidate for the development of SNEDDS formulation to enhance bioavailability, avoiding first pass metabolism by getting absorbed through the skin **[14]**. Therefore, the transdermal dosage form of LRCH formulate to minimize the oral degradation effects and to provide relatively consistent drug levels for prolonged periods.

The major problem associated with transdermal drug delivery is barrier properties of stratum corneum which is considered one of the most impermeable epithelia of the human body to exogenous substances.These permeation problems can be minimized by using a transdermal patch with nanoemulsion containing hydrogel. In prior studies, nanoemulsion as carrier system has been utilized for transdermal delivery of various drugs **[14, 15]**.

The present investigation was aimed to formulated SNEDDS of poorly water-soluble LRCH with statistical optimization method. Transdermal drug delivery was formulated by imbibing nanoemulgel in reservoir type patch for better and prolonged release of drug with overcoming the limitation of oral route delivery of LRCH.

2 MATERIAL AND METHODS

2.1 Materials:

Captex® 355 (Caprylic/Capric Triglyceride Medium Chain Triglyceride), Captex® 300 Low C6 (Caprylic/Capric Triglyceride Medium Chain Triglyceride), Capmul® MCM C8 (Mono- and di-glycerides of capric/ caprylic acids),Capmul-GMO (Long-chain mono-glycerides Glyceryl monooleate) Capmul PG-8 (PG fatty acid esters -PG monocaprylate), Capmul PG-12 (PG fatty acid esters -PG monolaurate/dilaurate), were gifted by Abitec Corporation, USA,

Imwitor 742 (Mono- and di-glycerides of capric/ caprylic acids) gifted by Sasol Germany. Sefsol 218 (PG fatty acid esters -PG monocaprylate) was obtained as gift sample from Nikko Chemicals Tokyo Japan. Peceol (Long-chain mono-glycerides Glyceryl monooleate), Maisine-35 (Glyceryl monolinoleate), Capryol 90 (PG fatty acid esters -PG monocaprylate), Lauroglycol 90 (PG fatty acid esters -PG monolaurate/dilaurate), Lauroglycol FCC(PG fatty acid esters -PG monolaurate/dilaurate) kindly supplied by Gattefosse India Pvt Ltd, Mumbai India.Labrafil® 2125 CS (Polyglycolyzed glycerides- Linoleoyl-macrogol glycerides), Labrafil 1944 CS

(Polyglycolyzed glycerides-Oleoyl macrogol glycerides), Labrasol®(Capryl-o-caproyl macrogol glyceride), Gelucire® 44/14 (Lauroyl macrogol glycerides), Cremophor RH 40 (POE hydrogenated castor oil-POE-40-hydrogenated castor oil), BASF India LimitedBandra (East), Mumbai, India. Transcutol® P (Glycol ethers - Diethylene glycol monoethyl ether), Solutol HS 15® (POE-stearate PEG-660-12-hydroxystearate), Cremphor® EL (POE castor oil POE-35-castor oil), was purchased from Sigma Aldrich Chemicals Pvt Ltd in Kushaiguda, Hyderabad, India. Olive oil, Soybean oil, Castor oil (Fixed oils), Tween® 80 (Polysorbates-POE-20-sorbitan monooleate), Tween 20(Polysorbates-POE-20-sorbitan monolaurate), Span® 80 (Sorbitan esters-Sorbitan monooleate), Span 20 (Sorbitan esters- Sorbitan monolaurate), Pluronic®/Lutrol F 68 (PEO–PPO– block-copolymers), Propylene glycol (Alkane diols and triols), Glycerol (Alkane diols and triols), PEG 200, PEG 400 (Polyethylene glycols), Plurol® Oleique CC 497 CG (Polyglycerol ester of oleic acid) were purchased from Loba chemicals. Pvt. Ltd. Mumbai, India and S.D. Fine Chem Ltd. Mumbai, India. All other chemicals used in the study were of analytical grade.

2.2 Methods:

2.2.1 Study of LRCH Solubility in Various Oils

To find out the right SNEDDS components with good solubilizing capacity for LRCH, saturation solubility was performed on different oils, surfactants and cosurfactants using the shake flask method **[16]**. Each of the selected solvents was added to a screw-cap tube (2 mL) followed by excess quantities of LRCH. The mixtures were capped and mixed for 5 min using a vortex mixer (REMI-Mumbai, India). The mixtures were then agitated at 150 rpm in a shaking water bath (REMI-4DC-Mumbai, India) at 40°C for 72 h to reach equilibrium. After reaching equilibrium, each tube was centrifuged at 5000 rpm for 10 min (Electro lab - KCM - 70M Mumbai, India). The supernatants were filtered using a membrane filter (0.45 μm, Whatman, Mumbai, India **[17]** and filtered solutions were suitably diluted with methanol and drug concentrations were determined using UV–Vis spectrophotometer (Shimadzu, UV-1800, Kyoto, Japan) at λ_{max} 236 nm. All measurements were done in triplicate and the solubility was expressed as the mean value (mg/mL) ± SD.] **[18]**.

2.2.2 Study of LRCH Solubility in Various Surfactants (Emulsification study)

Several surfactants were screened for emulsification ability of the selected oil phase. Surfactant was selected by two criteria as; the percentage of transparency (%transparency) and ease of emulsification. Briefly, 300 mg of the surfactants were added to 300 mg of the selected oily phase. The mixtures were gently heated at 50°C for homogenization of the components. Each mixture, 50 mg, was then diluted with distilled water to 50 mL in a stoppered conical flask. Ease of emulsification was judged by the number of flask inversions required to yield a homogenous emulsion **[19]**. The emulsions were allowed to stand for 2 h and their % transparency was evaluated at 694 nm by double-beam UV spectrophotometer (Shimadzu, UV-1800, Kyoto, Japan) using distilled water as a blank. The emulsions were furthermore observed visually for any turbidity or phase separation **[20]**.

2.2.3 Study of LRCH Solubility in Various Cosurfactants (Emulsification study)

Six co-surfactants were screened for SNEDDS formulation. The screening of the cosurfactants was conducted based on % transparency and ease of emulsification. Mixtures of 100 mg of the cosurfactant, 200 mg of the selected surfactant and 300 mg of the selected oil were prepared and evaluated similarly as described in the above section of surfactant selection **[19, 20]**.

2.2.4 Pseudoternary Phase Diagram for SMEDDS Formulation

Construction of the Ternary Phase Diagram based on the solubility and emulsification study, Capmul® MCM C8, Cremophor® RH 40 and Transcutol® P were selected as the oil, surfactant and co-surfactant, respectively. To determine the concentration of components for the existing range of SNEDDS, a Pseudoternary phase diagram was constructed using the water titration method at ambient temperature (25°C) **[21]**. The surfactant and co-surfactant were mixed in different volume ratios (1:3, 1:2 1:1, 2:1, and 3:1). Phase diagrams are constructed for each ratio **[22]**. Slow titration of distilled water is added (5% addition at a time) into the S_{mix}-oil mixture and the observation of the transition from clear to turbid point is noted down. The calculation is made to determine the percentage of water, oil and S_{mix} present at the point of turbidity. With the obtained individual percentage, a pseudo-ternary phase diagram is developed with the clear-solution region marked as best emulsification region **[23]**. The

Pseudoternary plot was constructed using the TRIPLOT V14 software **[24]**.

2.3 Method of Preparation of SNEDDS

Accurately weighed LRCH was placed in a screw-capped glass vial, and required quantity of oil, surfactant, and co-surfactant were added by using positive displacement pipette. The mixture was mixed by gentle stirring and vortex mixing at 40ºC on a magnetic stirrer at 300 rpm till LRCH dissolve **[25, 26]**. The mixture was stored at room temperature in the closed container until further use.

2.4 3^2 factorial design for optimization of formulation parameters of LRCH SNEDDS

The preliminary trials were carried out using several concentrations of oil and different concentration of surfactant/cosurfactant ratio. Capmul® MCM C8 was selected as oil, and Cremophor® RH 40: Transcutol® P (2:1) as a surfactant/cosurfactant ratio. Based on results of preliminary trials, the concentration of Capmul® MCM C8 oil (X1) and Concentration of Cremophor® RH 40: Transcutol® P (2:1) (X2) were taken as independent variables at three levels. The Globule size (Y1), Emulsification time (Y2), drug release at 15 minutes of LRCH (Y3) were considered as a dependent variable of SNEDDS. Multiple regression analysis, contour plot and 3D response surface plot were used to study the main and interaction effects of the variables on the responses **[5, 8]**. Factorial design batches were prepared as per **Table 1**.

Table 1: Formulation of factorial batches of LRCH SNEDDS

Factorial batches	Coded value of independent variable		Actual value of independent variable	
	Capmul® MCM C8 oil (X1)	Cremophor® RH 40: Transcutol® P (2:1) (X2)	Capmul® MCM C8 oil (X1)	Cremophor® RH 40: Transcutol® P (2:1) (X2)
LFB-1	-1	-1	0.6	1
LFB-2	-1	0	0.6	1.2
LFB-3	-1	1	0.6	1.4
LFB-4	0	-1	0.8	1
LFB-5	0	0	0.8	1.2
LFB-6	0	1	0.8	1.4
LFB-7	1	-1	1.0	1
LFB-8	1	0	1.0	1.2
LFB-9	1	1	1.0	1.4

2.5 Evaluation of LRCH SNEDDS

2.5.1 FTIR spectroscopy study:

FTIR Spectrum of pure drug and drug-excipients were obtained by FT-IR Spectrophotometer.

The spectrums of drug, excipients and Formulation were taken with the accumulation 24 scans and a resolution of $4cm^{-1}$ over the range of 400- 4000 cm. The spectrum of drug-excipient mixtures so obtained was compared with spectrum of pure drug for any interactions or Incompatibilities **[27]**.

2.5.2 Refractive Index and %Transmittance:

The Self-Nanoemulsifying system (SNEDDS) was added to 250 ml of purified water under continuous stirring (50-60 rpm) on a magnetic stirrer at room temperature. Refractive index of the formulation was measured by using an Abbe's Refractometer and % transmittance was measured at 694nm in UV-Visible spectrophotometer using water as a blank **[13]**.

2.5.3 Measurement of Globule Size, Polydispersity Index (PDI) and Zeta Potential

Globule size, Polydispersity index (PDI) and zeta potential of SNEDDS were determined using Zetasizer Nano ZS (Malvern Instruments, UK), which follows the principle of LASER light diffraction. A helium-neon gas laser having an intensity of 4 mW was the light source. Light scattering was monitored at 25°C at a 90° angle(17). SNEDDS was added (after 1:100 dilution) to the sample cell and put into the sample holder unit and measurement was carried out with the help of software of the same instrument **[28, 29]**.

2.5.4 Robustness test of SNEDDS

Robustness of SNEDDS to the dilution and effect of aqueous phase composition were studied using optimized LRCH SNEDDS composition. 1mL of LRCH SNEDDS were dispersed in 250 ml of aqueous phases (Distil water) with gentle stirring. Resulting Nanoemulsions were kept at 25 ± 2°C and evaluated for drug precipitation, phase separation over 24 hours **[28, 30]**.

2.5.5 Measurement of Viscosity of LRCH SNEDDS

Viscosity of SNEDDS comprising LRCH was measured by using Brookfield viscometer at 25°C. It was measured using S-61 spindle at 30 rpm before and after dilution with water (250 ml) in triplicates **[31]**.

2.5.6 Measurement of pH LRCH SNEDDS

pH of SNEDDS comprising LRCH was measured by using pH meter (Electrolab-India) at controlled room temperature. It was measured before and after dilution with water (250 ml) in triplicates **[21, 24]**.

2.5.7 Self-Emulsification and Precipitation Assessment

Evaluation of the self-emulsifying property of SNEDDS formulations was performed by visual assessment as previously reported. Different compositions were categorized on the speed of emulsification, clarity and apparent stability of the resultant emulsion. Visual assessment was performed by dropwise addition of pre-concentrate (SNEDDS) into 250 ml of distilled water. This was done in a glass beaker at room temperature, and contents

were gently stirred magnetically at 50-100rpm. Precipitation was evaluated by visual inspection of the resultant emulsion after 24 hours. The formulations were categorized as Clear or Non-clear and Stable, or Unstable **[32]**.

2.5.8 Thermodynamic Stability Studies:

SNEDDS was subjected to thermodynamic stability studies to access any phase separation and stability of the LRCH SNEDDS **[8, 24, 28]**

A) Centrifugation Study:

The formulation was centrifuged at 5000 rpm for 30 min. The resultant formulation was then checked for any instability problem, such as phase separation, creaming, cracking or drug precipitation.

B) Heating and Cooling Cycles:

The SNEDDS formulations were subjected to six heating-cooling cycles, between 4 °C and 40 °C, for 48 h. The resultant formulations were assessed for any physical instability like precipitation and phase separation.

C) Freeze-Thaw Cycles:

The SNEDDS formulations were subjected to four freeze-thaw cycles between -21 °C and 21 °C. Initially, the formulations were exposed at -21 °C in a deep-freezer for 24 h. Subsequently, the formulations were also thawed at 21 °C for 24 h and kept again in deep-freezer for the next cycle. The formulations were then observed for any physical change(s) such as phase separation and creaming.

2.5.9 Drug Content

LRCH from pre-weighed SNEDDS was extracted by dissolving in 25ml methanol. The methanolic extract was separated and LRCH content in the methanolic extract was analysed UV spectrophotometric method at 236 nm, against standard methanolic solution of LRCH **[20, 26]**.

2.5.10 In-Vitro Drug Release Study

In vitro drug release study was performed as drug dissolution studies. The dissolution test was performed in USP 24 type II dissolution test apparatus (Electrolab TDT-06P, India), containing 900 ml of dissolution medium (Phosphate buffer pH 6.8) maintained at 37 ± 0.5°C and stirred at 50 rpm. SNEDDS were directly added to the medium. Aliquots were collected periodically at 5, 10, 15, 20, 25 and 30 minutes and replaced with fresh dissolution medium. Aliquots, after filtration through Whatman filter paper (No. 41), were analyzed spectrophotometrically at 236 nm for LRCH content **[6, 23]**.

2.6 Formulation of the SNEDDS-based hydrogel of LRCH

The optimized LRCH SNEDDS formulation was incorporated into 1% w/v of Carbopol 941 to get a gel of the LRCH SNEDDS. Weighed quantity of the

Carbopol 941 was dissolved in 10 mL of distilled water and stirred thoroughly to get homogenous slurry. The optimized and stable LRCH SNEDDS was incorporated and mixed thoroughly and the pH was adjusted to neutral with triethanolamine. The control formulation was prepared by adding 0.1% w/w LRCH to phosphate-buffered at pH 6.8 and was gelled by the addition of Carbopol (1% w/w) **[15]**.

2.6.1 Measurement of viscosity

Viscosity is measured of the SNEDDS and the respective gel formed for all the formulations using Brookfield viscometer. Viscosity is measured using spindle no. S-62 **[33]**.

2.6.2 Drug content

The drug content of the LRCH SNEDSS based gel was determined by dissolving an amount of gel containing 10mg of the drug. The drug content was determined after appropriate dilutions at 236 nm by UV Spectrophotometer **[34]**.

2.7 Formulation and evaluation of the reservoir-type patch of SNEDDS based gel of LRCH

Transdermal patches (reservoir type) of LRCH were made-up by encapsulating the LRCH gel preparation within a shallow compartment made of a hollow ring-shaped device and drug-impermeable backing membrane (laminated aluminium foil). A cellulose acetate membrane was stuck onto the impermeable-backing membrane to bring the transdermal patch in intimate contact with the skin. The device was closed by a release liner on the open side **[35]**.

2.7.1 In-vitro skin permeation studies

2.7.1.1 Preparation of skin

The skin was obtained from local slaughter house (abdominal skin). The epidermis was prepared surgically by heat separation technique, which involved soaking the entire abdominal skin in water at 60ºC for 45 sec, followed by careful removal of the epidermis. The epidermis was washed with water and used for in-vitro skin permeability studies **[36]**.

2.7.1.2 Set-up for in-vitro skin permeation studies

In vitro skin permeation studies were performed on a Franz diffusion cell with an effective diffusional area of 1 cm^2 and 85 ml of receiver chamber capacity using pig abdominal skin. The skin was mounted between the donor and receiver compartment of the Franz diffusion cell, where the stratum corneum side faced the donor compartment and the dermal side faced the receiver compartment. The donor compartment was empty and the receiver chamber was filled with phosphate-buffered pH 6.8. The receiver fluid was stirred with a magnetic rotor at a speed of 100 rpm and the temperature was

maintained at 37 ºC. Formulated patch is placed into a donor compartment. Samples were withdrawn at regular interval (1, 2, 3, 4, 5, 6, 7 and 24 hours), filtered through 0.45 membrane filter and analysed spectrophotometrically at 236 nm for LRCH content **[33, 36]**.

2.7.1.3 Permeation data analysis

The cumulative amount of drug permeated through the skin (µg/cm^2) was plotted as a function of time (t) for each formulation.

Drug flux (permeation rate) at steady state (J_{ss}) was calculated by dividing the slope of the linear portion of the graph by the area of the diffusion cell **[33]**.

The permeability coefficient (K_p) was calculated by dividing J_{ss} by the initial concentration of drug in the donor cell (C_0):

$$\mathbf{Kp} = \frac{J_{ss}}{C_0} \text{----------2}$$

Enhancement ratio (E_r) was calculated by dividing the flux (J_{ss}) of the respective formulation by the flux (J_{ss}) of the control formulation:

$$E_r = \frac{J_{ss}\ of\ Formulation}{J_{ss} of\ Control\ formulation} \text{---------3}$$

2.8 Similarity factor (f2):

Mathematical comparison of dissolution data to quantify observed differences in the rate and extent of drug release as influenced by formulation and process variables was performed according to the model-independent approach of Moore and Flanner **[37]**. A similarity factor (f2) was calculated from mean dissolution data using the following equation:

$$f_2 = 50 \log\{[\,1 + \left(\frac{1}{n}\right)\sum_{t=1}^{n}(R_t - T_t)^2\,]^{-0.5} \text{ x } 100\}$$

-------1

where a log is a logarithm to the base 10, n is the number of time points, ∑ is a summation over all time points, Rt is the mean dissolution value of the reference profile at time t and Tt is the mean dissolution value of the test profile at the same time point. The US FDA draft guidance document contains more information on the similarity factor (f2). The value of the similarity factor (f2) between 50 and 100 suggests that the two dissolution profiles are similar.

2.9 Stability Study of LRCH SNEDDS

Physical and chemical and stability of LRCH SNEDDS was assessed at and 25 ± 3°C/60 ± 5% (room temperature) and 40 ± 2°C/75 ± 5% RH as per ICH guidelines (24,26,38). LRCH SNEDDS were stored in a glass vial for 6 months. Samples were withdrawn at 0, 1, 3 and 6 months and assessed for physical change, globule size, emulsification time, drug content, and *in-vitro* drug release.

3 RESULTS AND DISCUSSION

3.1 Selection of oil phase:

Solubility studies were designed for selecting a suitable oily phase for the development of LRCH SNEDDS. The solubility of pure drug was found to be

0.0016 mg/ml in water. In the present investigation, the selection of oil for the preparation of SNEDDS was done based on their ability to solubilize the maximum amount of drug. This might be attributed to the fact that in SNEDDS drug should be in its dissolved state, as this form has been reported to possess a greater concentration of drug. The high concentration gradient provides a driving force for the permeation of drug through the GI tract as well as other biological membranes **[24]** Maximum solubility of LRCH (89.09 mg/ml) was found in Capmul® MCM C8 **(Figure 1)**. hence it was selected for the future investigation. On based of result of solubility it was accomplished that Capmul® MCM C8 could solubilize the target amount of LRCH (10 mg) at a relatively small amount of 112 µL.

3.2 Selection of surfactant (solubility study)

To observe the part of surfactants in drug solubilization the solubility studies of LRCH was attended in different surfactants individually and their results are summarized in **Table 2** and comparative graph is given in **Figure 2**. Highest solubility for LRCH was found in Cremophor® RH 40 (168.79 mg/ ml). However, the selection of surfactant for SNEDDS was not done based on solubility studies since it was strongly believed that surfactant plays a vital role in the emulsification of the oil phase. Good solubility of drug in surfactant was considered as an added advantage as this feature may prevent drug precipitation during storage

3.3 Selection of surfactant (emulsification study)

In the present investigation, non-ionic surfactants were selected since they are known to be less affected by pH change, generally regarded as safe and are biocompatible. Ionic surfactants were excluded from the study due to toxicological concerns **[20]**. Evaluation of SNEDDS was done by perceiving quantitative parameters like %T and ease of emulsification (no. of flask inversions) after their subsequent emulsification in distilled water **[39]**. The data of emulsification study of Capmul® MCM C8 recommended that both grades of Cremophor (Cremophor® EL and Cremophor® RH 40) were excellent emulsifier among all surfactants. **(Figure 2)**. As per the literature, Cremophor® RH 40has been utilized in one of the few marketed SEDDS products and have so many biological advantages compared to Cremophor® EL. Hence, in the present investigation Cremophor® RH 40 was selected as surfactant for the emulsification of LRCH-loaded SNEDDS.

3.4 Selection of Cosurfactant (solubility study)

To observe the part of Cosurfactants in drug solubilization the solubility studies of LRCH was attended in different cosurfactants individually and their results are summarized in **Table 2** and comparatives graph is given in **Figure 3**. Highest solubility for LRCH was found in Transcutol® P (393.52 mg/ml). Addition of a co-surfactant to the surfactant-containing formulation was reported to improve dispersibility and drug absorption from the formulation **[40]**. Among all; the Transcutol® P exhibited highest emulsification efficiency with 5 flask inversion and maximum percent transmittance 100 % **[41]**.

3.5 Construction of Pseudo-Ternary Phase Diagram

Ternary phase diagrams were constructed to identify the self-nanoemulsifying regions and also to establish the optimum concentrations of oil, surfactant and co-surfactant **(Figure 4)**. From the phase diagrams, it was observed that as increasing the concentration of surfactant increased the self-nanoemulsifying region. Emulsification region decreased with increasing the concentration of co-surfactant. Efficiency of self-nano emulsification was good when the surfactant concentration was more than 50% and as the concentrations of oil increases (above 45%) showed the phase separation of SNEDDS formulation **[28]**. The maximum self-nanoemulsifying region was to be observed with the ratio of 2:1. Based on the ternary phase diagram, levels for the SNEDDS components was established containing 30-45% Capmul MCT C8, 40-70% cremophore RH 40 and 0-30% Transcutol P. It has been reported that the drug incorporated in the SNEDDS may have some effect on the self-nanoemulsifying performance. No significant differences were found in self-nanoemulsifying performance when compared with the corresponding formulations with LRCH **[17, 18]**.

3.6 Evaluation of LRCH SNEDDS formulations.

The results of refractive index and % transmittance of full factorial design formulae was shown in **Table 3** and was found in the range of 1.315 ± 0.0045 to 1.370 ± 0.0090 and 93.67 ± 1.53 % to 100.00 ± 0.00 % respectively. There was no significant difference in the refractive index values of the formulations tested without and with drug. The refractive index values close to that of the water (1.333) prove the isotropicity of the system **[42]**. The LRCH-SNEDD optimized formulation gave the smallest globule size (40 ± 4.23 nm, mean ± SD, n = 3) than other SNEDDS

formulations, while the PDI obtained was 0.23 ± 0.01 **(Table 2)**. Both size and PDI showed that LRCH-SNEDDS is a good nano-formulation as the size is less than 100 nm and PDI is less than 0.4. The charge of oil droplets in SNEDDS was negative due to the presence of free fatty acids; the zeta potential of the optimized formulation was -23.9 ± 0.42 (mean ± SD, n = 3). In general, the zeta potential value of ±30 mV is sufficient for the stability of a nanosuspension. In our formulation, it is -23.9 ± 0.42 which means it complies with the requirement of the zeta potential for stability **(Figure 5)**. All the diluted systems exhibited stable at pH and volume of dilution medium. Additionally, the all the systems were considered to be robust against dilution as it did not show any signs of phase separation and drug precipitation even after 24 h of storage **[20]**. The viscosity of the undiluted and diluted batches of LRCH SNEDDS were found to be in rage of 94.89 ± 2.08 cps to 136.13 ± 1.13 cps and 1.03 ± 0.016 cps to 1.11 ± 0.115 cps respectively at 25 °C. The pH of the undiluted and diluted batches of LRCH SNEDDS were found to be in rage of 7.191 ± 0.06 to 7.408 ± 0.16 and 6.858 ± 0.54 to 7.171 ± 0.06 respectively **(Table 3)**. The study revealed excellent stability of optimized batch of LRCH SNEDDS with no signs of phase separation or precipitation at various stress conditions studied **[22]**. The results revealed that drug content of all the batches was near to 100 % and the deviation in the results was less than 5 % which complied the standard of official pharmacopoeia. Batch LFB-6 shows highest percentage drug content.

All experimental design batches of LRCH SNEDDS demonstrated significant enhancement in the dissolution rate as compared to pure LRCH and Marketed product. The dissolution pattern of the optimized batch of LRCH SNEDDS released 96.43% of within 15 min compared to only 12.2% for pure LRCH and 19. 74 % of marketed product **(Figure 7a)**. Based on the experimental design, the factor combinations resulted in different responses observed and evaluated. From these results it can be concluded that batch LFB-6 yielded higher drug release within 15 min (>99%), acceptable globule size (23.45 nm), higher % transmittance (100%) and lower emulsification time (12.01sec) for the SNEDDS of lercanidipine compared to other formulation. Hence formulation LFB6 was consider as an optimized formulation among the all full factorial batches and was used for future study.

3.7 Optimization with factorial design.

The 3^2 factorial design was employed using concentration of Capmul® MCM C8 oil and concentration of Cremophor® RH 40:

Transcutol® P (2:1) surfactant/Cosurfactant as independent variable X1 and X2 respectively. The Globule size (GS) (Y1), Emulsification time (ET) (Y2), and drug release at 15 minutes (Q15) (Y3) of LRCH were selected as dependent variables. The polynomial equations can be used to draw conclusions after considering the magnitude of coefficients and the mathematical sign carried: positive or negative. Positive value indicates positive influence of factor on response while negative value indicates inverse relationship between variables and response **(Table 4)**.

Multiple regression analysis was carried out for the responses using MS Excel. The reduced model was obtained by using significant terms ($p > 0.05$ was considered non-significant and such termed were neglected) for all the responses. The contour and response surface plot were constructed using Design Expert version 11 (Demo version).

3.7.1 Regression analysis of Globule size

A full model equation of globule size (Y_{GS}) was written as below Equation.

Y1 (Y_{GS}) = 40.298-4.740X1-20.452X2+0.037X1X2+25.31X1X1+3.89X2X2 --------4

(r2 = 0.99974)

The P value for the variable X_1 and X_2 were 2.815×10^{-4} and 3.534×10^{-6} respectively ($P< 0.05$), it indicated that both variables shown significant effect on Globule size of the formulation. The b_1 co-efficient have negative sign value indicated that as the concentration of oil increase in the system the globule size of the LRCH SNEDDS was reduce but upto certain extend and also magnitude of coefficient is less compared to factors X_2; similarly b_2 co-efficient have negative sign indicated that as the concentration of S_{mix} ratio increased in the system the size of globules was decrease and magnitude of coefficient is so high compared to factor X_1 it indicated that X_2 factors having greater effect on globule size of SNEDDS.

3.7.2 Regression analysis of Emulsification time

A full model equation of emulsification time (Y_{ET}) was written in below Equation.

Y2 (Y_{ET}) = 27.987 + 5.803X1 – 15.561X2 + 1.104X1X2 + 26.887X1X1 – 0.272X2X2----5

(r2 = 0.99896)

The P-value for the variable X_1 and X_2 were 4.602×10^{-5} and 0.00084 respectively ($P< 0.05$), it indicated that both variables shown significant effect on emulsification time of the formulation. The b_1 co-efficient has positive sign value indicated that as the concentration of oil increase in the system the emulsification time of the LRCH SNEDDS was increased. Similarly, b_2 co-efficient has negative sign indicated that as the concentration of S_{mix} ratio increased in

the system the time of emulsification of the system was decrease and magnitude of the coefficient is so high compared to factor X_1 it indicated that X_2 factors having a greater effect on emulsification time of SNEDDS. b_{11} shows positive sign with a high magnitude of coefficient designated greater effect on emulsification time compared to other factors in the system.

3.7.3 Regression analysis of Q15

A full model equation of emulsification time (Y_{Q15}) was written below Equation.

Y3 (Y_{Q15}) = 95.342 - 1.212X1 + 5.748X2 + 0.385X1X2 - 9.018X1X1 - 1.938X2X2----------6

(r2 = 0.98083)

The P-value for the variable X_2 was 4.069 x 10^{-6} ($P< 0.05$), it indicated that X_2 variables shown significant effect on % drug release from the formulation. The b_1 co-efficient has negative sign value with a low magnitude of coefficient indicated that as the concentration of oil increase in the system the % drug release of the LRCH SNEDDS was decreased. Similarly, b_2 co-efficient has positive sign indicated that as the concentration of S_{mix} ratio increased in the system the % drug release of the system was increase and magnitude of the coefficient is so high compared to factor X_1 it indicated that X_2 factors having a greater effect on the release of drug from LRCH SNEDDS formulations. b_{11} shows a negative sign with a high magnitude of coefficient designated greater effect on % drug release compared to other factors in the system.

3.7.4 Contour plot and surface response plot of LRCH factorial design formulation

Contour plot and surface response plot of LRCH factorial design formulation shown in **Figure 8**.

Contour plot and surface response plot of Globule size of LRCH SNEDDS showed the relationship of X1 factors and X2 factors in liner. As the concentration of X1 increased in formulation globule sized was decreased but after some level was increased. Contour plot and surface response plot of emulsification time of LRCH SNEDDS shown that as the concentration of X1 increased in the system it increased the time of emulsification of the formulations. Contour plot and surface response plot of Q15 of LRCH SNEDDS showed that the concentration of X2 has greater effects on the release of drug from the formulations.

By using numerical optimization, a desirable value for each input factor and response can be selected. Optimized formulation was selected by arbitrarily fixing the criteria of 27 – 33 nm of the Globule size (GS), 16 to 22 Second emulsification time (ET), 97 to 99 % drug

released at 15 minutes for LRCH SNEDDS formulations. These constraints were shown in figure no. 27 and **Table 5** for the LRCH SNEDDS formulation. The recommended concentrations of the independent variables were calculated by the Design-Expert software using desirability criteria approach.

The Nanoemulgel formulation of both LOB-1 and LFB-6 were prepared as per the procedure described in methodology sections. The optimized LRCH SNEDDS formulation was incorporated into 1% of Carbopol 941 to get a Nanoemulgel of the LRCH SNEDDS. The control formulation was prepared by adding 0.1% w/w LRCH to phosphate-buffered at pH 6.8 and was gelled by the addition of Carbopol (1% w/w). formulated Nanoemulgel was subjected to evaluate various parameters like rheological characteristic, in vitro diffusions study etc.

3.8 Ex vivo permeation study:

Nanoemulgel was incorporated in the transdermal patch and were used to evaluate the ex vivo permeation through the pig abdominal skin.

Permeability parameters like steady-state flux (Jss), permeability coefficient (Kp), and enhancement ratio (Er) were calculated. The permeability parameters of different formulations are given in **Table 6**. It was observed that the calculated flux of optimized formulation was found to be more as compared to pure drug gel formulation.

3.9 Stability study:

The change in globule size, Emulsification time, drug content and drug release at 15 minutes for LRCH was carried out by the procedure described under methodology sections. The globule size of LRCH SNEDDS was changed insignificantly in accelerated stability condition. Whereas emulsification time was slightly increased. The drug content was evaluated in both the conditions. It was concluded that there was no significant change in the drug amount for 6 months. The optimized batch was found to be chemically stable. Drug release study was performed at 15 minutes. The results revealed that there was more than 95% of drug dissolution in 15 minutes for 6 months. Hence on the evaluation of the all parameter it was concluded that the optimized batch LFB-6 was found to be the most stable formulation.

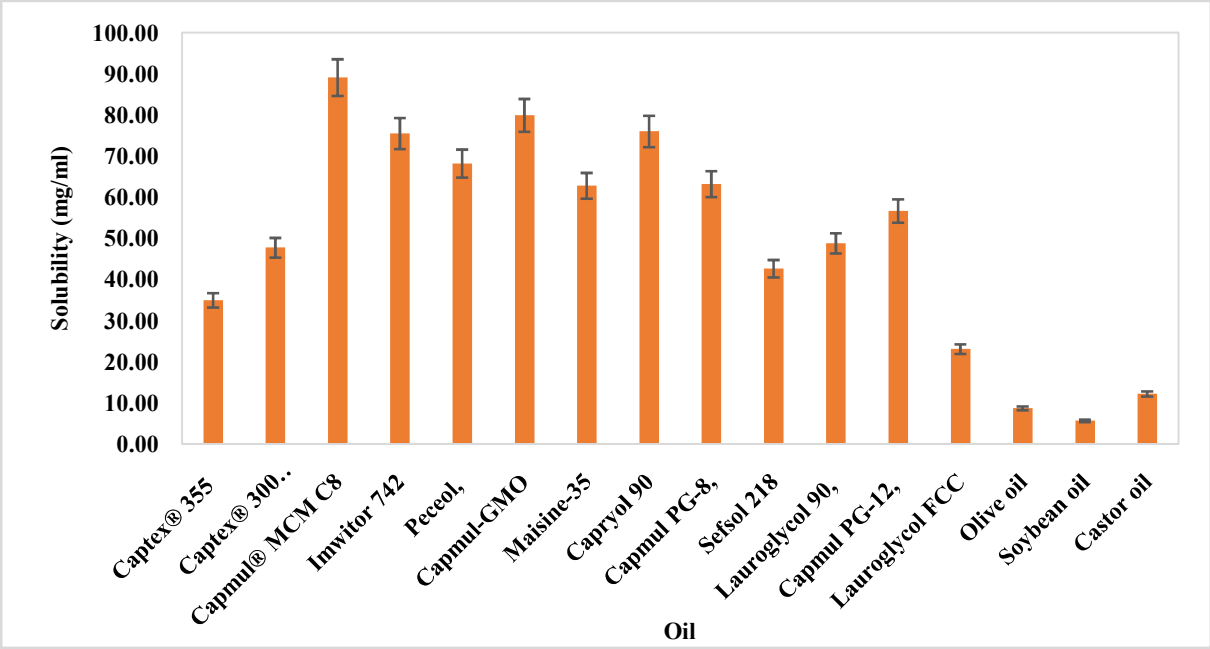

Figure 1: Solubility study of LRCH in various oil

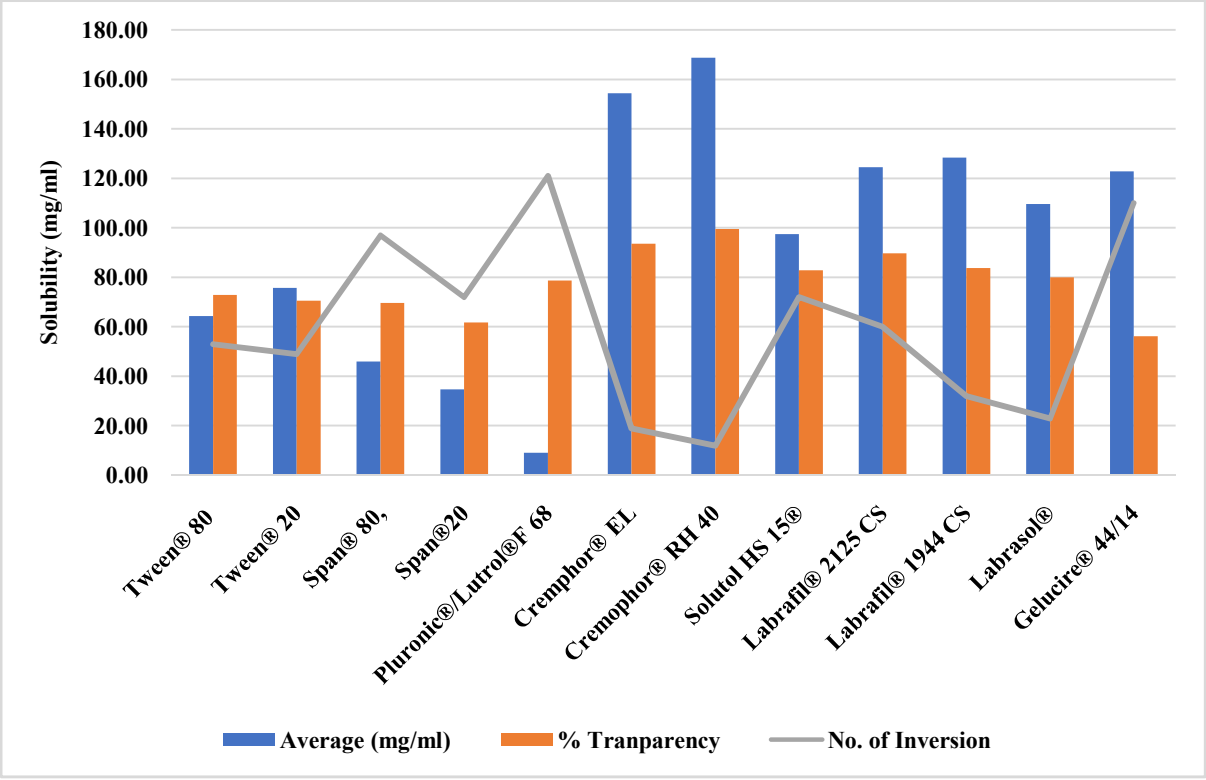

Figure 2: Solubility, emulsification time and no of inversion of LRCH in Surfactants

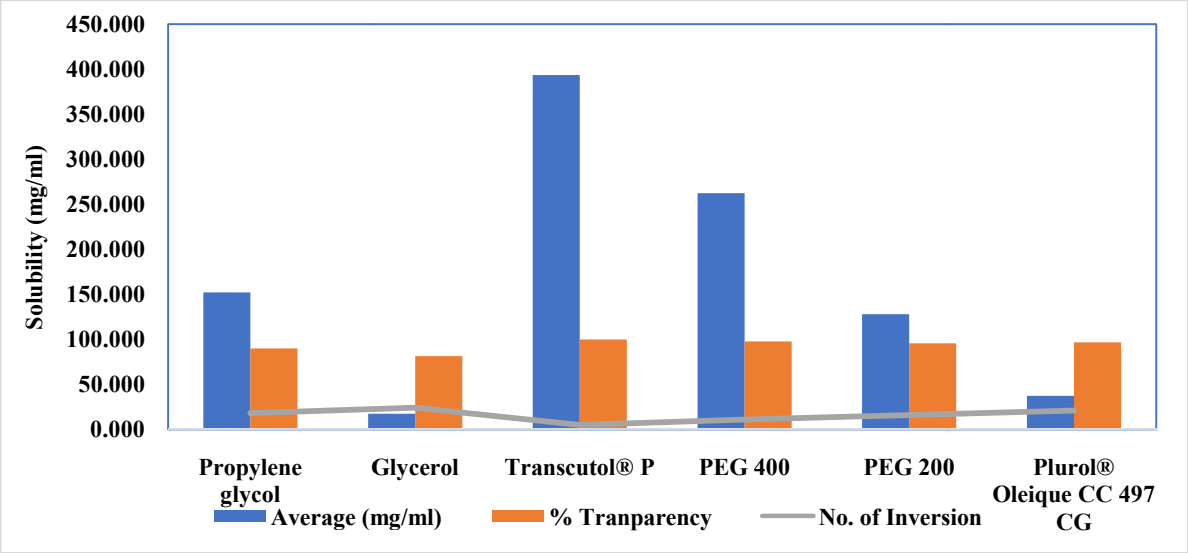

Figure 3: Solubility study of LRCH in cosurfactants

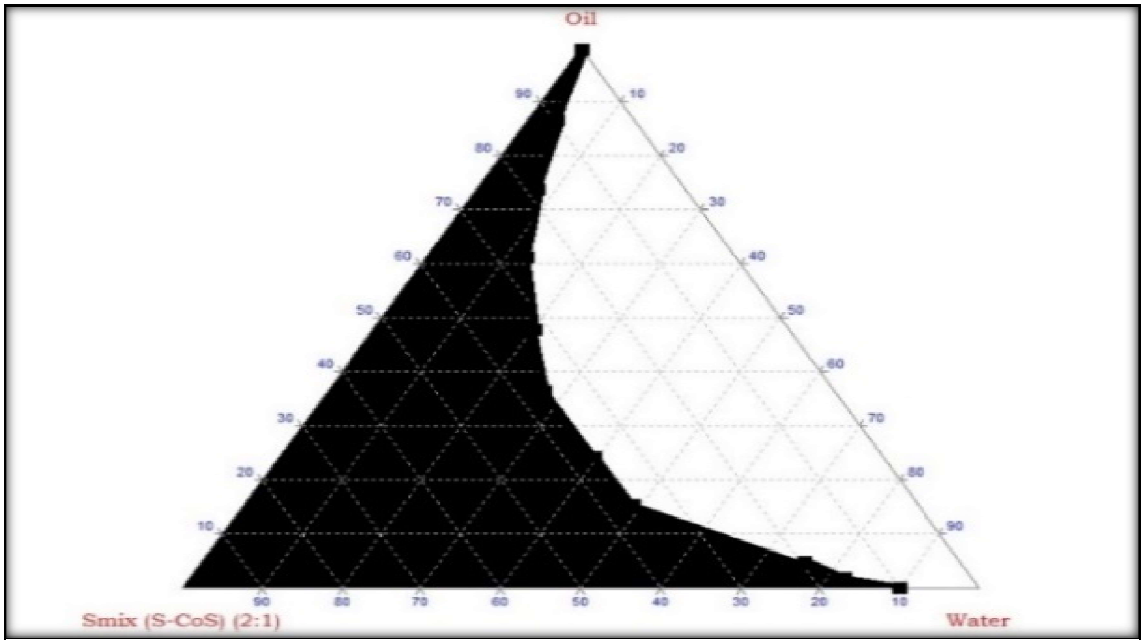

Figure 4: Pseudo-ternary phase diagrams indicating emulsification region (shaded area) of Capmul® MCM C8 (oil), Cremophor® RH 40 (surfactant), and Transcutol® P(co-surfactant) of S mix ratios indicated in parts (S mix 2:1)

Table 2: Evaluation parameter of LRCH SNEDDS formulations

Factorial Formulae	Refractive Index#	%Transmittance#	Polydispersity Index# (PDI)	Zeta Potential# (mV)
LFB-1	1.357 ± 0.0015	93.67 ± 1.53	0.432 ± 0.0035	-14.41 ± 0.072
LFB-2	1.360 ± 0.0032	94.00 ± 2.00	0.323 ± 0.0015	-17.32 ± 0.025
LFB-3	1.370 ± 0.0090	96.67 ± 2.52	0.225 ± 0.0020	-19.32 ± 0.035
LFB-4	1.360 ± 0.0072	97.00 ± 1.00	0.375 ± 0.0036	-16.70 ± 0.026
LFB-5	1.355 ± 0.0038	98.67 ± 0.58	0.261 ± 0.0030	-21.92 ± 0.020
LFB-6	1.315 ± 0.0045	100.00 ± 0.00	0.192 ± 0.0006	-26.12 ± 0.006
LFB-7	1.323 ± 0.0035	94.67 ± 1.15	0.424 ± 0.0025	-15.30 ± 0.026
LFB-8	1.356 ± 0.0036	96.00 ± 1.00	0.305 ± 0.0026	-20.64 ± 0.015
LFB-9	1.345 ± 0.0040	97.33 ± 0.58	0.255 ± 0.0020	-24.34 ± 0.040

Table 3: Evaluation parameter of LRCH SNEDDS formulations

Factorial Formulae	Viscosity (cp)#		pH#		Drug Content of LRCH SNEDDS (%)
	Undiluted	Diluted	Undiluted	Diluted	
LFB-1	94.89±2.08	1.03±0.016	7.191±0.06	6.858±0.54	98.18±2.33
LFB-2	108.17±0.50	1.04±0.019	7.240±0.03	7.006±0.70	98.29±0.62
LFB-3	126.10±1.53	1.10±0.122	7.201±0.07	6.868±0.54	96.36±1.00
LFB-4	102.86±0.81	1.03±0.007	7.271±0.07	7.011±0.08	97.62±1.01
LFB-5	118.91±0.50	1.06±0.031	7.310±0.09	6.910±0.51	99.88±0.93
LFB-6	131.84±0.06	1.05±0.040	7.238±0.02	7.171±0.06	100.01±0.12
LFB-7	112.51±1.53	1.05±0.017	7.364±0.16	6.931±0.35	99.02±0.47
LFB-8	125.19±0.50	1.11±0.115	7.408±0.16	6.941±0.69	97.47±1.16
LFB-9	136.13±1.13	1.17±0.231	7.394±0.15	7.054±0.05	99.48±0.92

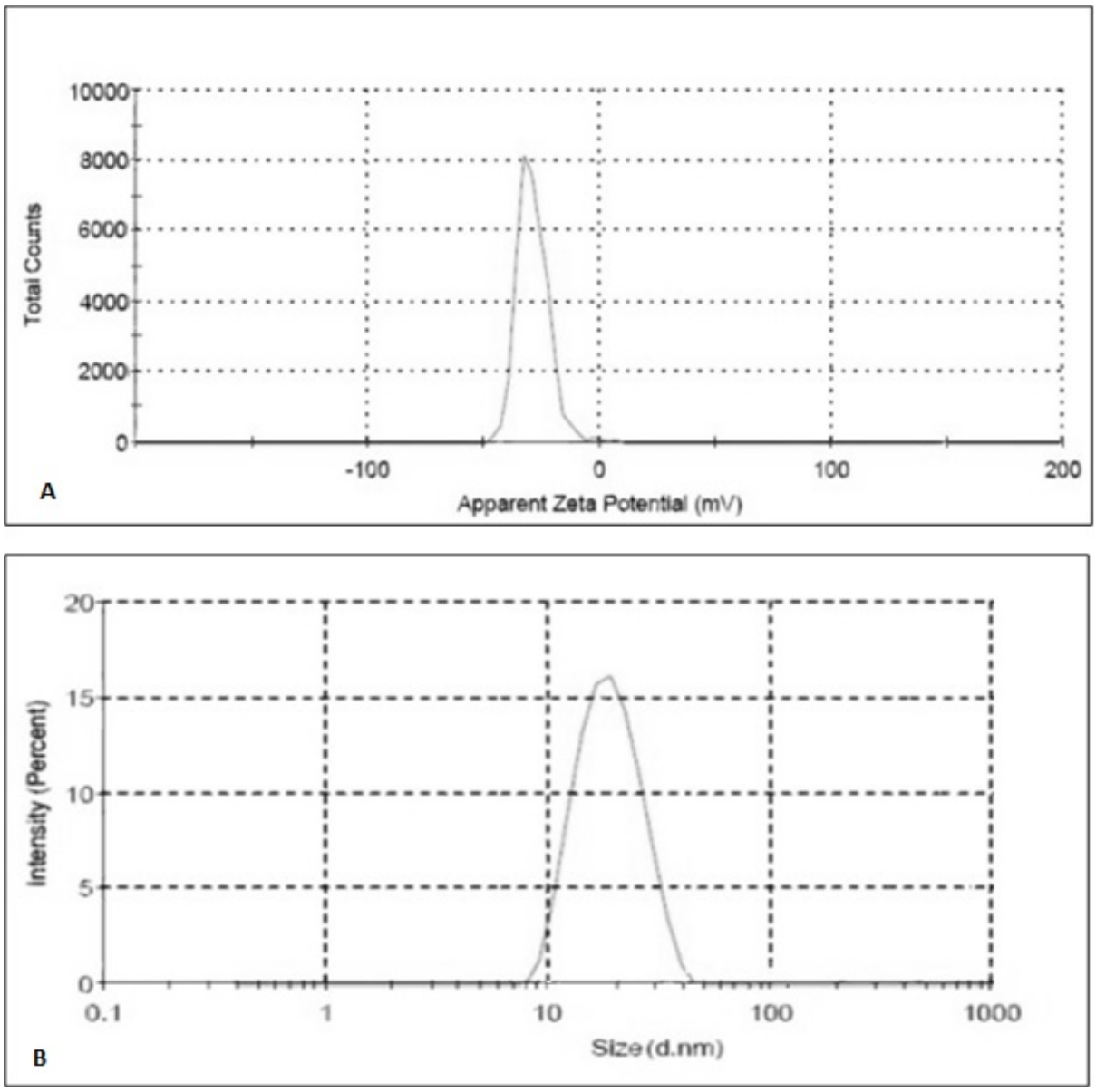

Figure 5: (A) Size distribution graphs (B) zeta potential

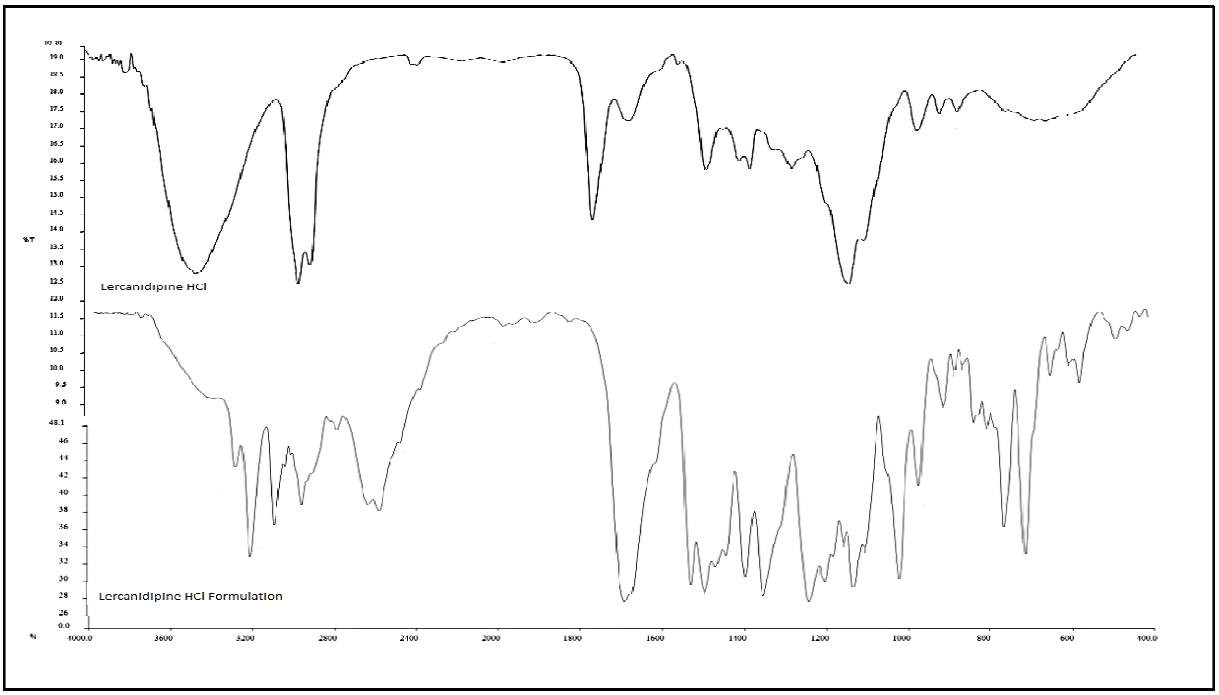

Figure 6: FTIR spectra of pure drug and SNEDDS

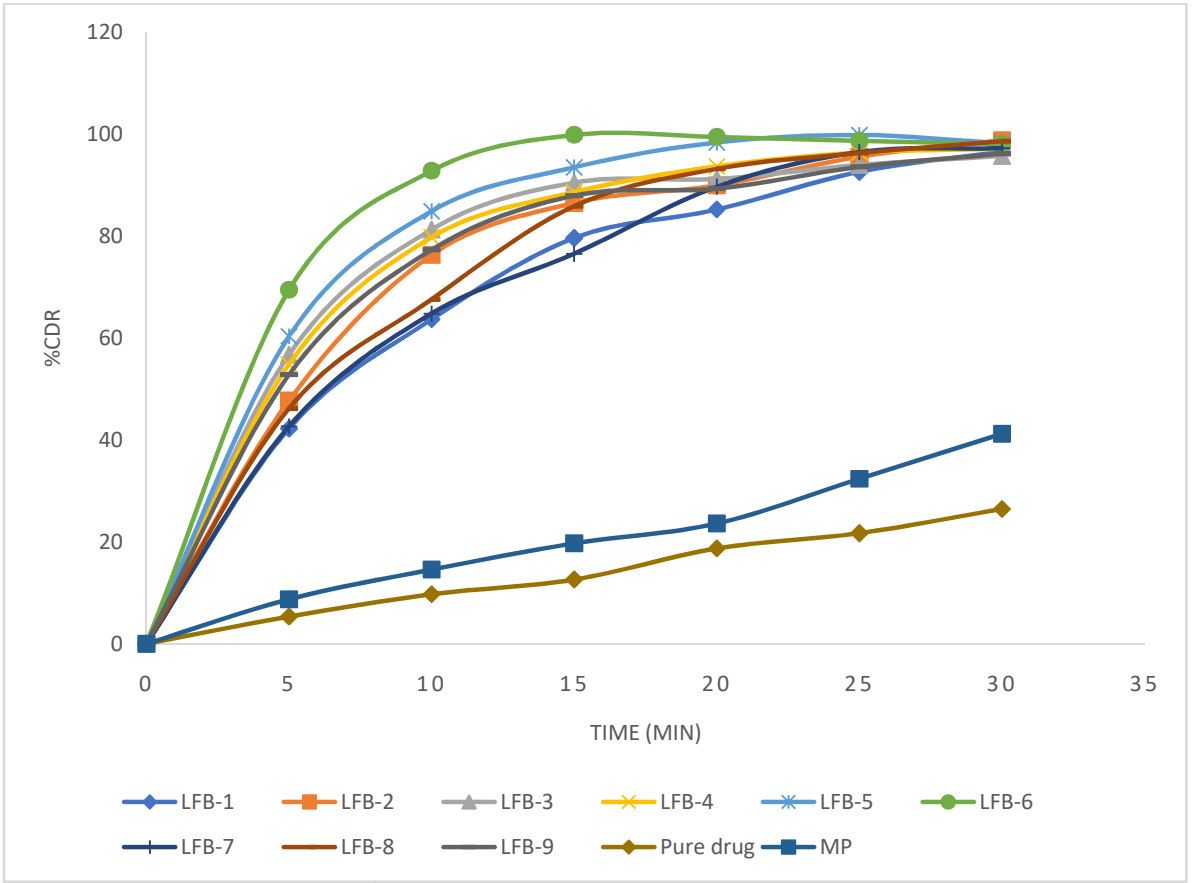

Figure 7: *In vitro* diffusion profile the factorial design batches, pure drug and marketed product

Table 4: The runs and responses for 3^2full factorial batches of LRCH SNEDDS

Factorial Formulae	Coded value of independent variable		Actual value of independent variable		Responses of dependent variables of full factorial design		
	(X1)	(X2)	(X1)	(X2)	GS (Y1)	ET (Y2)	Q15 (Y3)
LFB-1	-1	-1	0.6	1	94.36	65.67	79.67
LFB-2	-1	0	0.6	1.2	70.83	48.33	88.53
LFB-3	-1	1	0.6	1.4	53.63	32.67	90.53
LFB-4	0	-1	0.8	1	64.85	43.79	88.69
LFB-5	0	0	0.8	1.2	40.38	27.61	93.54
LFB-6	0	1	0.8	1.4	23.45	12.01	99.92
LFB-7	1	-1	1.0	1	85.33	74.14	76.57
LFB-8	1	0	1.0	1.2	60.30	61.79	85.92
LFB-9	1	1	1.0	1.4	44.75	45.56	88.97

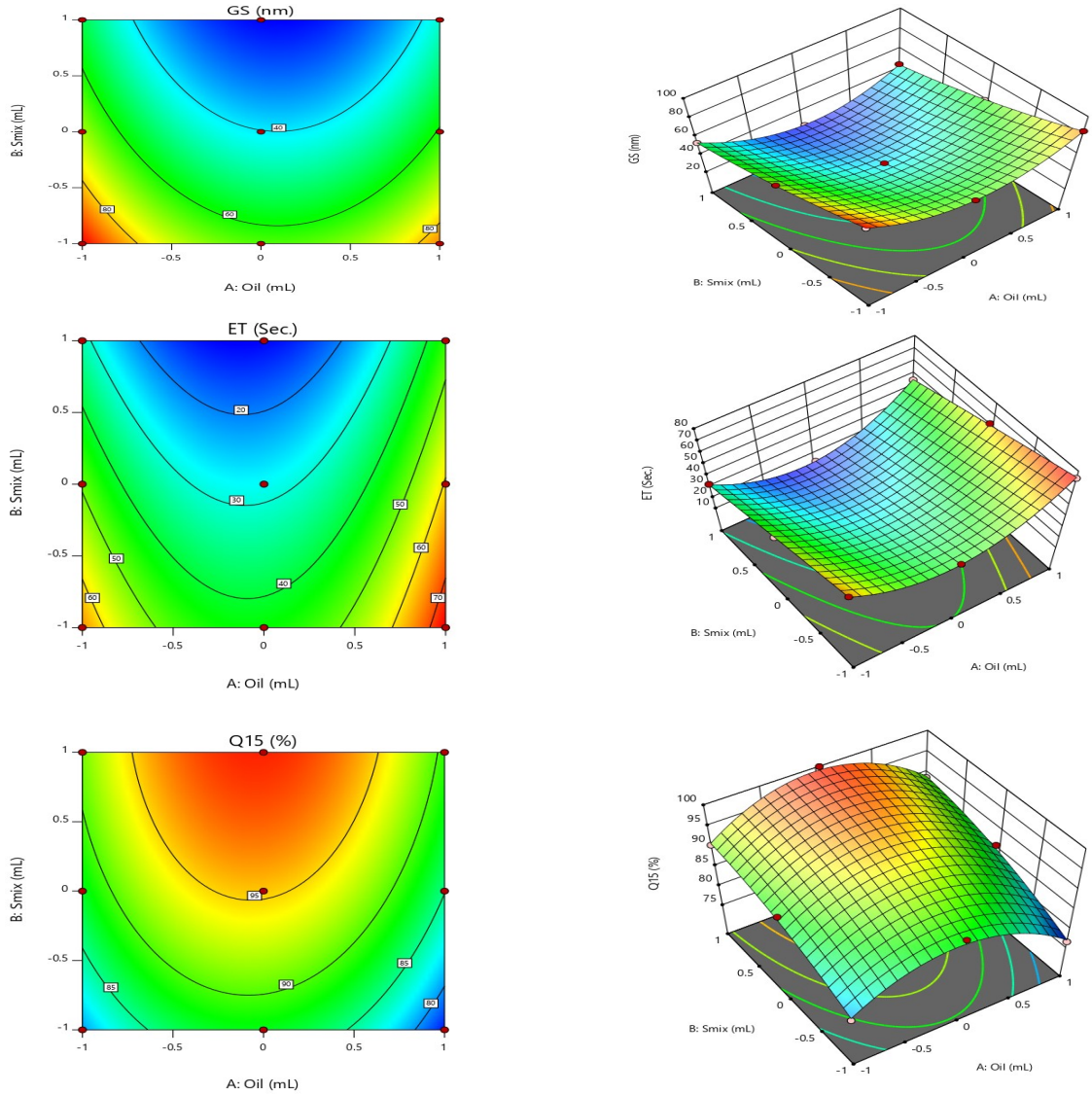

Figure 8 : contour plot and 3D Response surface plot of LRCH SNEDDS

Table 5: Formulation of Optimized batch of factorial design and desirability batch suggested by software

Desirability batch suggested by software (LOB-1)				Optimized batch of factorial design (LFB-6)			
X1		X2		X1		X2	
Coded Value	Actual Value (ml)	Coded Value	Actual Value (ml)	Coded Value	Actual Value (ml)	Coded Value	Actual Value (ml)
-0.1265	0.7747	0.4703	1.29406	0	0.8	1	1.4

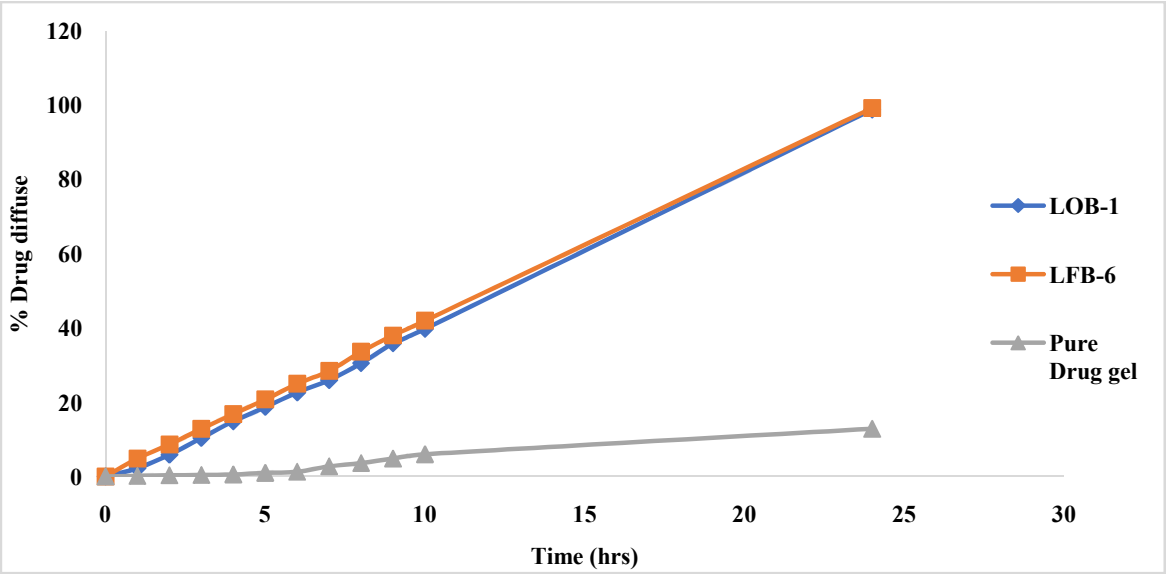

Figure 9: Ex-vivo diffusion of LRCH from optimized formulans and pure drug gel

Table 6: Calculated flux, permeation coefficient and enhancement ratio of various patch formulations

Formulation Code	Slope	Flux Jss (µg/cm^2/hr)	Permeation coefficient (Kp)	Enhancement Ratio
LOB-1	371.41	371.41	37.141	7.142
LFB-6	375.48	375.48	37.548	7.220
Pure Drug gel	52.001	52.001	5.2001	-

4 CONCLUSION

SNEDDS is a promising tool for transdermal drug delivery, present investigation was focused on the development of thermodynamically stable SNEDDS nanogel for transdermal delivery of LRCH. Optimization was done by 3^2 factorial design. The optimized formulation LFB-6 contained 36.36% Capmul® MCM C8 as an oil, 42.42% Cremophor® RH 40 as a surfactant, and 21.22% Transcutol® P as a cosurfactant. Optimized batch suggested by software-based in desirability criteria LOB-1 conation 37.24 % Capmul® MCM C8 as an oil, 41.70 % Cremophor® RH 40 as a surfactant, and 20.85 % Transcutol® P as a cosurfactant. Emulsification time and globule size of optimized formulation was about 12.01 second and 23.45nm respectively. Optimized formulation did not show any kind of phase separation or precipitation upon dilutions. pH of the formulation was found to be 7 which indicated it was

neutral. Invitro dissolution studies have shown that optimized formulation can release the drug faster than pure drug and marked formulation. Accelerated stability study further revealed that optimized formulation was stable. Permeation of LRCH in then a nono emulgel loaded transdermal patch was compared with hydrogel of pure which exhibited significantly higher ($P< 0.05$) cumulative amount of drug permeated and flux.

Therefore, the present investigation confirmed that nanoemulgel base transdermal patch formulation can be used as a feasible alternative to conventional formulations of LRCH with advanced permeation characteristics for transdermal application in order to avoid the first pass metabolism.

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