Design and Characterization of Self Nano-emulsifying Drug Delivery System for Terbinafine Hydrochloride.

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Abstract– Aim of this research work is to develop a self nano-emulsifying drug delivery system (SNEDDS) for Terbinafine hydrochloride, which is an antifungal agent, has poor aqueous solubility and bioavailability. In this work SNEDDS were formulated by using Soybean oil, Tween 80 and PEG 400 as oil, surfactant and co-surfactant respectively, for that; solubility study, pseudo ternary phase diagram and Box- Behnken designs were applied to get the optimized formulation. Characterization of prepared batches was done in that thermodynamic stability study, globule size analysis, zeta potential determination and in-vitro dissolution studies were performed, after this in –vitro data was fitted in various kinetic models, from that it was observed that the optimized batch is following Hixson-Crowell model. Additionally in-silico pharmacokinetic studies were carried out to determine pharmacokinetic parameters in simulated conditions. After evaluation it is observed that the prepared formulation is stable and from in-silico study, globule size and zeta potential range of optimized batch it was observed that absorption may occur by lymphatic uptake mechanism. Due to this it avoids first pass metabolism and shows improved bioavailability.

Keywords– SNEDDS; Terbinafine hydrochloride; Box- Behenken design; Lymphatic uptake

I. INTRODUCTION

About 40% of newly discovered drug molecules are having poor water solubility; therefore this becomes a major hurdle for formulation of such drugs into the dosage forms which can be taken orally. Oral route of drug administration is a predominant over other routes because of its ease, simplicity and patient acceptance. Various drugs showing different activities are formulated in oral dosage form to get easy patient acceptance and also due to low cost manufacturing processes. But there are many factors which must be considered while formulating the oral dosage form of drug like, solubility of drug. Because of poor solubility the drug shows dissolution problems and further bioavailability issues [1]. To overcome this problem many approaches were utilized like; micronization, nanonization, solid solutions, solid dispersion, use of complexing agent, lipid formulations. Lipid formulations contains drug dissolved in a two or more excipients like triglycerides or partial triglycerides, surfactants and co-surfactants. When such prepared lipid formulation is administered orally it comes in contact with gastric fluid due to mild agitation of peristaltic movement emulsion get formed; which reduces the time required for dissolution of drug from its solid state to solution which is a rate limiting step for most of the absorption processes of drugs. In stomach it forms a colloidal dispersion and release of drug from this system is carried out with the help of lipid digestion [2]. In this study Terbinafine hydrochloride was used as model drug which is an allylamine antifungal agent. This drug is used to treat Pityriasis versicolor, fungal nail infections and ringworm including jock itch and athelete's foot. Terbinafine hydrochloride inhibits ergosterol synthesis by inhibiting the fungal squalene monooxygenase, an

enzyme that is part of fungal cell wall synthesis pathway. It is either taken by orally in the form of tablet and granules or applied topically as a cream or ointment. But the cream or ointment is not effective in nail infections. Terbinafine hydrochloride is poorly soluble in water and its oral bioavailability is very less. But this drug is ideal for formulating into the SNEDDS because it has log p value above 5 and Terbinafine hydrochloride is lipophilic in nature. Objective of this study is to formulate Terbinafine hydrochloride loaded SNEDDS to improve the dissolution and oral bioavailability of this poorly water soluble drug. In addition Terbinafine hydrochloride loaded SNEDDS were compared with pure drug and marketed formulation.

II. MATERIALS AND METHODS

2.1 Materials

Terbinafine hydrochloride, a model drug was obtained from Aurochem Pharmaceuticals, Pvt. Ltd., Mumbai as a gift sample. Soybean oil, castor oil, arachis oil and Sesame oil were purchased from SD fine chemicals, Mumbai. Tween 20, Tween 60 and Tween 80 were purchased from Loba Chemie, Pvt. Ltd., Mumbai. PEG 400 and PEG 200 were purchased from Hi media Labs, Mumbai. All other chemicals used were of analytical and laboratory grade.

2.2 Methods

2.2.1 Solubility studies for excipients selection

The saturation solubility of Terbinafine hydrochloride in various oils, surfactants and co-surfactants was determined. An excess amount of Terbinafine hydrochloride was added to each glass vial containing 2 ml of oil, surfactant and co-surfactant. The vials were then kept in vortex shaker at room temperature for 48 hr to reach the equilibrium. After 48 hr these vials are centrifuged at 3000 rpm for 20 min and the supernatants were separated and diluted suitably with methanol; further analyzed by using UV-Visible spectrophotometer (Shimadzu 1800, Japan) at λ_{max} of 283 nm. From this solubility study excipients were selected for further use [3].

2.2.2 Construction of pseudo-ternary phase diagram

Pseudo-ternary phase diagrams were plotted to get self-emulsifying region. The ternary diagrams were constructed by using water titration method. Various ratios of surfactant and co-surfactants were taken like 1:1, 2:1 and 3:1 respectively. Every S-mix was blended with selected oil to give weight ratio 9:1, 8:2, 7:3, 6:4, 5:5, 4:6, 3:7, 2:8, 9:1 (W/W) by using magnetic stirrer. These mixtures were titrated slowly with distilled water and visually inspected for transformation from turbid to transparent or transparent to turbid this was considered as end point of titration [5]. From this data ternary phase diagrams were constructed by using CHEMIX software. The high percentage of self emulsifying region was selected for further use.

2.3 Formulation and optimization by using Box-Behnken design

Three factors, three levels and 17 runs Box-Behnken experimental design was employed by using Design Expert 7.0 software to formulate liquid SNEDDS. The concentration of soybean oil (X1), Tween 80 (X2) and PEG 400 (X3) were selected as independent variables, while self-emulsification time in sec (Y1) and turbidity in NTU (Y2) were selected as responses. Response surface analysis was carried out to study the effects of different independent variables on the observed responses. The dependant and independent variables are listed in Table 1. Weighed quantity of Terbinafine hydrochloride (Dose = 250 mg) was added to oil and S-mix mixture and heated up to 40°C for 30 min with continuous stirring on magnetic stirrer to form a homogeneous mixture. The prepared liquid SNEDDS were stored in glass container with screw cap at room temperature until further use [6].

Table 1 Factors studied using Box-Behnken experimental design

Independent variables	Levels (ml)		
	High	Medium	Low
X_1=Amount of oil (soybean oil)	1	0.75	0.5
X_2=Amount of surfactant (Tween 80)	7	6.5	6
X_3=Amount of co-surfactant (PEG 400)	3.5	2.75	2

2.4 In-silico studies

For the study GastroPlus™ software was used. The main purpose behind this study was to know the pharmacokinetic parameters like absorption, distribution, elimination and toxicity of drug and formulation (SNEDDS). Inputs used in this software are log P value of drug and aqueous solubility of drug and solubility of drug in formulation. From this data all parameters were determined.

2.5 Characterization of liquid SNEDDS

2.5.1 Physical appearance, pH and viscosity

Physical appearance was evaluated for clarity and homogeneity by visual assessment against light and dark background. The pH of optimized formulation was determined by using digital pH meter (Systronics µ pH system 362) which was previously calibrated with the help of standard buffer solutions of pH 4 and pH 7. The formulation was diluted 100 times with distilled water and analysed for pH. Viscosity of optimized batch was determined by using Brookfield viscometer by using spindle no. 61 at 50rpm.

2.5.2 Refractive index

The optical clarity of liquid SNEDDS were determined in terms of refractive index by using Abbe's refractometer (Weswox AR-12 Abbes refractometer).

2.5.3 Thermodynamic stability

The formulations were subjected to different thermodynamic stability studies. First one is heating cooling cycle; six cycles between temperature 4°C and 45°C with storage at each temperature not less than 48 hr was studied. Those formulations, which were stable at these temperatures, were tested for centrifugation. Passed formulations were centrifuged at 3000 rpm for 30 min. Those formulations that didn't show any phase separation were taken for the freeze thaw stress study. Three freeze thaw cycles between -21°C and +25°C with storage at each temperature for not less than 48 hr was done [13]. Those formulations which were stable after this stress test were selected for further tests.

2.5.4 Dispersibility test

One ml of liquid SNEDDS from each formulation was taken, and added to 500 ml of distilled water at 37°C with constant stirring at 50 rpm into USP type II apparatus. The SNEDDS were observed for formation of stable emulsion. The emulsions formed were visually observed for phase clarity and times required for the formation of emulsions were noted. From the appearance and time required for formation of emulsion; these systems were graded by using following grading system [8]

Grade A- Rapidly forming (within 1 min) micro-emulsion having a clear or bluish appearance

Grade B- Rapidly forming, slightly less clear micro-emulsion having a bluish white appearance

Grade C- Fine milky micro-emulsion that formed within 2 min

Grade D- Dull grayish white emulsion having slightly oily appearance that is slow to emulsify (longer than 2 min).

Grade E- Poor or minimal emulsification with large oil globules present on the surface.

2.5.5 Turbidity measurement

Turbidity of these formed emulsions were measured by digital nephelo/turbidity meter (Systronics 132, India) in nephelometric turbidity units (NTU) with approximated accuracy of ± 3% of FSD in 0-1 and 0-1000 NTU as specified by the manufacturer. Previously the device was calibrated with formazin standards.

2.5.6 Globule size, size distribution and zeta potential

Malvern zetasizer (Zetasizer nano ZS90) was used to determine globule size, polydispersity index and zeta potential. Liquid SNEDDS were diluted 1000 times with distilled water and shaken gently to form a fine emulsion and measured further. The values of z-average were used for this study.

2.5.7 Comparative in-vitro drug release studies

This study was carried out in between pure drug, marketed formulation and optimized formulation filled in hard gelatin capsule (size 00) by using USP type II dissolution apparatus. Dissolution media used for this was 900 ml of simulated gastric fluid without enzymes of pH 1.2 at 50 rpm and temperature was maintained at 37 ± 0.5°C. Accurately 5 ml of aliquots were withdrawn at specific time intervals of 5, 10, 15, 30, 45, 60, 90 and 120 min and same amount of fresh media was replaced to maintain the sink condition. Aliquots were filtered and analyzed by using UV-Visible spectrophotometer at λ_{max} of 283 nm. [9]

2.5.8 Drug release kinetics study

Mathematical model plays important role in evaluation of drug release mechanism and improvement in the formulation. Choosing the proper mathematical model is crucial to know a system with optimum drug release. To study the drug release kinetics of optimized batch, pure drug and marketed formulation; data obtained from in-vitro dissolution study was plotted in different release kinetics models. The used mathematical models were zero order kinetic model, first order kinetic model, Higuchi model, Korsemeyer-Peppas model and Hixson–Crowell model.

*Zero order release pattern***:** Zero order kinetic models define the drug release system, in which drug release rate is independent of its concentration. Mathematical equation of zero order model can be given as-

$$C = C_0 - K_0 t \quad (1)$$

Where, C=amount of drug release (assuming that release occur rapidly after the drug dissolved), C_0=Initial amount of drug in solution (usually, $C_0 = 0$), K_0 = Zero order rate constant and t= time. This relationship of zero order kinetic model is useful to define dissolution rate of modified-release dosage forms, like transdermal drug delivery systems,

coated matrix tablets of poorly water-soluble drugs, osmotic drug delivery system. In this study, cumulative amount of drug released was plotted against time to obtain zero order release pattern.

*First order release pattern***:** First order kinetic model describes adsorption and elimination of certain drugs. Mathematical equation of first order kinetic model is as follows-

$$\text{Log } C = \text{Log } C_0 - Kt/2.303 \quad (2)$$

Where, C_0 = Initial concentration of drug, K = First order rate constant, t = time, slope = K/2.303. This slope value is obtained by plotting log cumulative percentage of drug remaining versus time. The first order kinetic model is beneficial to explain the drug dissolved in pharmaceutical dosage forms containing water-soluble drugs in porous matrices. For this study, we have plotted log cumulative percentages of drug remaining versus time to obtain first order release pattern.

Higuchi release pattern: Higuchi model is used to describe drug release from matrix systems. In addition, this model is also used to describe different geometrics and porous systems. Mathematical equation of Higuchi model can be given as-

$$C = [D\,(2qt - C_s)\,C_s t]^{1/2} \quad (3)$$

Where, C=total amount of drug release per unit area of the matrix (mg/cm^2), D=diffusion coefficient for the drug in the matrix (cm^2/hr), qt=total amount of drug in a unit volume of matrix (mg/cm^3), C_s=dimensional solubility of drug in the polymer matrix (mg/cm^3) and t=time. Higuchi model is useful to describe dissolution of drugs from a modified release pharmaceutical dosage forms like, transdermal systems and matrix tablets with water-soluble drugs. Data obtained in this study were plotted as cumulative percentage of drug release versus square root of time to obtain Higuchi release pattern.

*Korsmeyer-Peppas release pattern***:** Korsmeyer-Peppas model evaluate drug release from a polymeric system. Usually, first 60% of the drug release data is fitted in Korsemeyer-Peppas model to elucidate the mechanism of drug release. Mathematical equation of Korsmeyer-Peppas model can be expressed as-

$$C_t/C_\infty = kt^n \quad (4)$$

Where, C_t/C_∞=fraction of drug release at time t, k=rate constant and 'n' =release exponent. The n value is employed to characterize different release for cylindrical shaped matrices. For slab matrix, if exponent is less than 0.5, then diffusion mechanism is Quasi Fickian; if exponent is exact 0.5 then it is Fickian diffusion and if $0.5 < n < 1.0$, then it is anomalous transport (Non Fickian diffusion). If 'n' is 1.0, it is case II transport and if $n > 1.0$, then it is super case II transport [20]. Data obtained in this study were plotted as log cumulative percentage of drug release versus log time to obtain Korsmeyer-Peppas release pattern.

Hixson-Crowell release pattern: Hixson-Crowell model explains the drug release mechanism from a system, when, there is change in surface area and diameter of particle.

Mathematical equation of Hixson-Crowell model can be given as-

$$C_0^{1/3} - C_t^{1/3} = K_{HC}t \quad (5)$$

Where, C_t=amount of drug released in time t, C_0=initial amount of drug in the pharmaceutical dosage form and K_{HC}=rate constant for Hixson-Crowell equation. When Hixson-Crowell is used to describe a system, it is considered that the release rate of drug particles is limited by the dissolution rate and not by the diffusion which might take place during the polymeric matrix. In addition, to describe a release pattern, this model considers that the surface of the drug particles lessen during the dissolution. To study the Hixson-Crowell kinetics of release, data obtained from this study was plotted as cube root of initial concentration minus the cube root of percent remaining versus time.

III. RESULTS AND DISCUSSIONS

3.1 Solubility studies

Solubility of Terbinafine hydrochloride in various oils, surfactants and co-surfactants is given in Table 2. Terbinafine showed maximum solubility in soybean oil, Tween 80 and PEG 400, therefore these three ingredients or excipients were selected for the formulation and construction of pseudo-ternary phase diagram.

Table 2 Solubility of Terbinafine hydrochloride in various oils, surfactants and co-surfactant

Solvents	Solubility (µg/ml)	
oils	Arachis oil	7.076
	Sesame oil	11.417
	Soybean oil	30.911
	Castor oil	10.941
Surfactant	Tween 20	2.717
	Tween 60	12.847
	Tween 80	39.111
Co-surfactant	PEG 400	25.017
	PEG 200	5.186

3.2 Construction of pseudo-ternary phase diagram

Two phase diagrams are shown in Figure.1. The ternary phase diagrams were constructed to determine concentration ranges of components. All the components were first converted into weight/weight percentage and then entered the values in software to get the ternary plots. The colored region in ternary phase diagrams presents the area of self-emulsification. When 1:1 ratio of surfactant and co-surfactant were titrated with distilled water, this ratio failed to form emulsions in different combinations therefore ternary phase diagram was not constructed for this ratio. The second Figure 1 (b) shows larger area of self-emulsification around 43% than Figure 1 (a) therefore this ratio of surfactant and co-surfactant (3:1) was chosen.

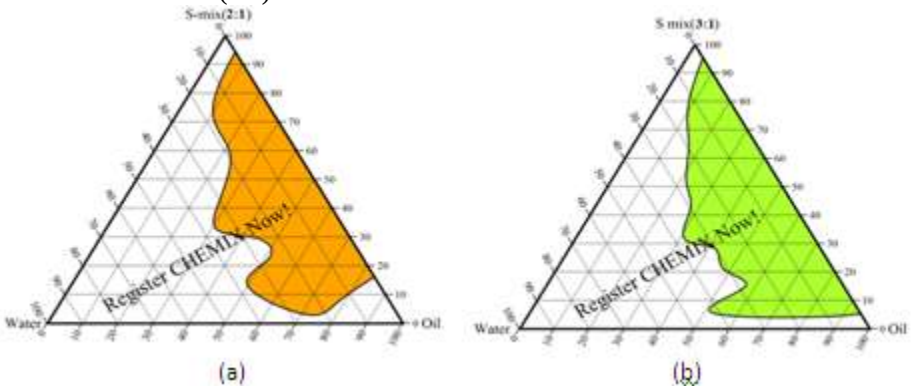

Figure 1. Pseudoternary phase diagram of various ratios of oil to s-mix (a) (2:1), (b) (3:1)

3.3 Optimization of SNEDDS by Box-Behnken design

A Box- Behnken experimental design was used with 3 independent variables at 3 levels and 2 dependant variables or responses. And also to get optimized formulation with robustness and high quality characteristics. A total 17 formulations were prepared as per the experimental design and evaluated for responses like self emulsification time and turbidity as shown in Table 3. For all 17 formulations dependant variables showed wide variation; for self-emulsification time (Y_1) it was observed from 19.23 to 63.74 s and for turbidity (Y_2) it was observed from10.6 to 454.7 NTU. The values of the coefficients X_1, X_2 and X_3 are related to the effect of these variables on the response. A positive sign of coefficients indicates a synergistic effect while a negative term indicates inverse effect on response [10]. To identify the significance of effects and interactions between independent variables and responses, analysis of variance (ANOVA) was performed for each responses. It was found that quadratic model was most suitable.

Table 3 Observed responses for 17 formulations of Box-behenken design

Runs	Soybean oil (ml) X_1	Tween 80 (ml) X_2	PEG 400 (ml) X_3	Self-emulsification time (Sec) Y_1	Turbidity (NTU) Y_2
F1	0.75	7.00	2.00	22.65	15.4
F2	0.75	6.00	2.75	48.56	153.3
F3	1.00	6.00	3.50	46.75	246.1
F4	0.75	5.00	3.50	41.84	418.5
F5	0.50	6.00	2.00	46.52	108.3
F6	0.50	6.00	3.50	20.14	17.5
F7	0.75	7.00	3.50	24.48	14.6
F8	1.00	6.00	2.00	54.27	341.7
F9	0.75	6.00	2.75	43.61	378.4
F10	1.00	7.00	2.75	19.23	11.2
F11	0.75	5.00	2.00	52.4	454.7
F12	0.75	6.00	2.75	45.38	237.8
F13	1.00	5.00	2.75	63.74	405.6
F14	0.50	7.00	2.75	19.86	10.6
F15	0.75	6.00	2.75	37.78	376.2
F16	0.50	5.00	2.75	36.88	302.6
F17	0.75	6.00	2.75	38.14	162.4

Self-emulsification time (SET) was used to measure the time required for formation of emulsion when it comes in contact with aqueous media. Main effect observed was statistically significant (p values < 0.05), amount of Tween 80 is negative (-12.83) suggesting an inversely proportional relationship with SET. It means concentration of surfactant when increases it showed smaller value of SET. [11] Turbidity is used to determine the transparency of formed emulsion and as the emulsion tends to clarity globule size tends to decrease. Therefore from the ANOVA it was observed that, surfactants showed negative value (-191.20) therefore having inversely proportion with the turbidity hence as concentration of surfactant increases turbidity of formulation decreases. But contrary so-surfactant (PEG 400) showed positive values (27.93) it therefore it has direct correlation with turbidity of emulsion that is, when concentration of co-surfactant increases turbidity also increases. Figure 2(a) indicates interaction between oil (soybean oil) and surfactant (Tween 80) on SET with increase in amount of surfactant lowering of SET was observed and as surfactant concentration decreases and amount of oil increases SET also increases. Same was observed in case of turbidity which is shown in Figure 2 (b).

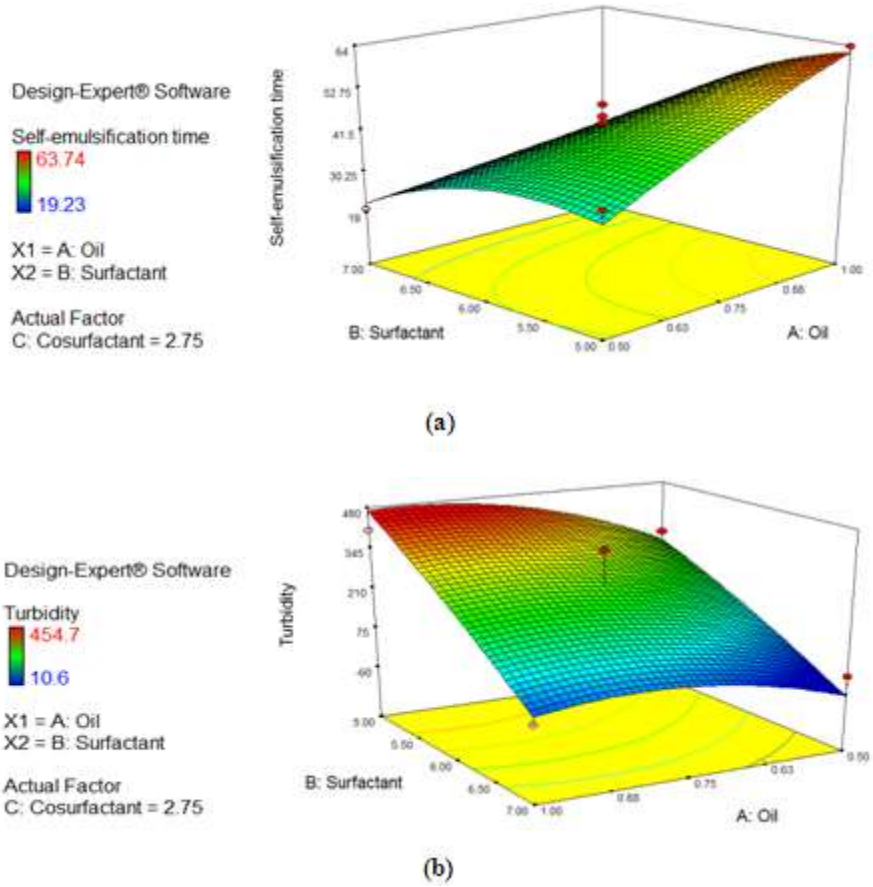

Figure 2. Response surface plots (a) interaction between X_1 and X_2 on Y_1 (b) interaction between X_1 and X_2 on Y_2.

After getting all results levels selected for X_1, X_2 and X_3 were 1, 7 and 2.75 (which is the composition of F10) respectively which gives theoretical values of 19.23 s (SET) and 11.2 NTU (Turbidity). Fresh formulation was prepared using above levels of independent variables. The observed values were found to be 18.29 s for SET and 11.5 NTU for turbidity which were close with the theoretical values. [12]

3.4 In-silico studies

After applying software we get the values of different parameters which are given in table 4 from that we get the idea about the increase in oral bioavailability was observed in optimized formulation as compared to pure drug. Oral bioavailability of pure drug was found to be 40% and when this drug was formulated into SNEDDS; oral bioavailability increases to 65.55% due to the oily component present in the formula. Figure 3 is of SNEDDS plasma concentration and time profile. It was observed that low T_{max} value (1.25 h) and higher C_{max} value (0.338µg/ml) of formulation as compared to pure drug indicating maximum drug absorption [15]. From the values

of %FDP and $C_{max\ liver}$ it was observed that drug may be absorbed into lymphatic pathway because both values were smaller as compared to pure drug.

Table 4 Comparison of pharmacokinetic parameters between drug and formulation

	Predicted values	
Parameters	**Drug**	**Formulation**
% FA	100%	100%
% FDP	100%	30%
% F	40%	65.55%
C max	0.18 µg/ml	0.338 µg/ml
C max liver	3.68 µg/ml	0.62 µg/ml
T max	2.10 h	1.25 h
AUC_{0-8}	4.72 µg h /ml	6.61 µg h /ml

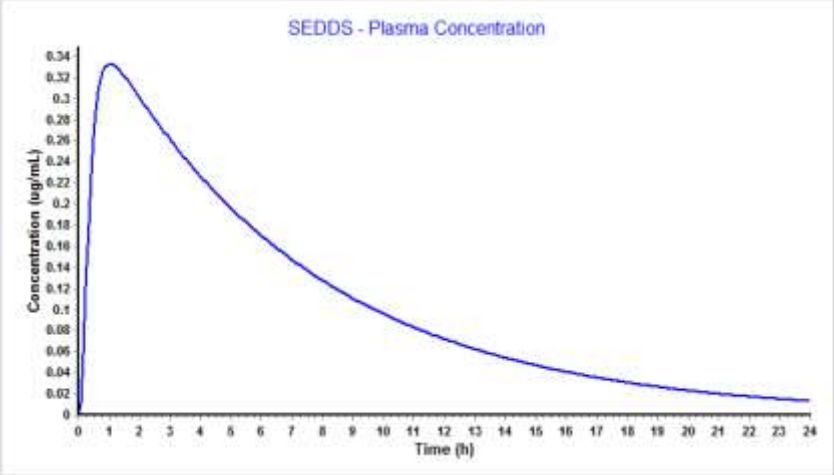

Figure 3. Plasma concentration time profile.

3.5 Characterization of liquid SNEDDS

3.5.1 Physical appearance, pH and viscosity

Physical appearance was clear; pH of optimized batch was found to be 5.12 and viscosity required for filling into the hard gelatin capsule is should be less than 10000 cPs [18]. Viscosity of optimized formulation was found to be 409.2 cPs therefore formulation can be filled in hard gelatin capsules.

3.5.2 Refractive index

Refractive index of optimized batch was found to be 1.355 which is close to the refractive index of water (1.333). Therefore it indicates the optimized formulation is stable.

3.5.3 Thermodynamic stability studies

For checking the physical stability of formulations this study was carried out from 17 formulations F6, F10 and F14 remained stable throughout the test, which were did not show any phase separation or precipitation. But all other formulations failed this test and phase separation was observed.

3.5.4 Dispersibility test

This test was performed to evaluate the self-emulsification time of each formulation for optimization; values for this were given in Table 3. To evaluate the grade of formed emulsion grading system were used; according to that optimized batch was of grade A that is; rapidly forming (within 1 min) micro-emulsion, having a clear or bluish appearance.

3.5.5 Turbidity measurement

From the value of turbidity one can predict the globule size of formed emulsion whether it is in nano size range or micro size range. This test was performed to get the optimized batch with small globule size. Values of each formulation were given in Table 3.

3.5.6 Globule size, size distribution and zeta potential

Globule size of emulsion plays important role in absorption and also in stability. Globule size of optimized formulation was found to be 171.8 nm (Figure. 4) which is within the range of nano-emulsion (20-200nm) and polydispersity index (PDI) was found to be 0.2787 which indicates that the droplets were highly dispersed in system and signifies higher stability. Zeta potential of optimized batch was found to be -24.07 mV (Figure. 5) negative potential around particles shows improved lymphatic uptake of system as compared with positive potential [19].

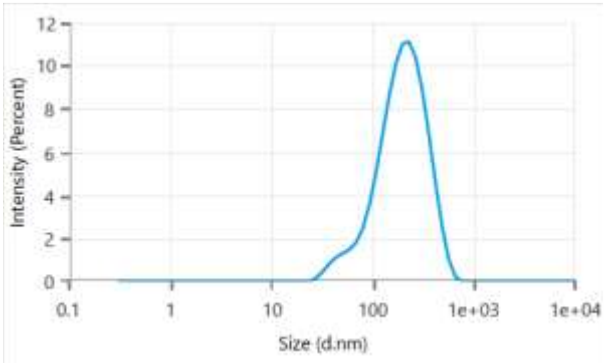

Figure 4. Globule size distribution graph of optimized batch.

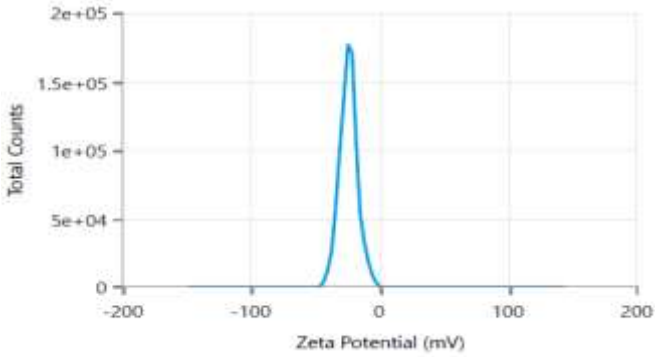

Figure 5. Zeta potential of optimized batch.

3.5.7 Comparative in-vitro drug release study

The in-vitro release study was performed in between pure drug, marketed formulation and optimized batch filled in hard gelatin capsule by using dissolution studies as shown in (Figure. 6). Drug release from the SNEDDS was found to be greater than pure drug and marketed formulation. Two step release pattern was observed for SNEDDS formulation; in first part release is very fast and reaches up to approximately 83% within 20min. due to fast formation of emulsion. Further the release was sustained. But the marketed formulation showed only one step release while this occurs very slowly. Within 20 min marketed formulation showed only 55%. The pure drug showed very less dissolution than marketed and SNEDDS. This indicates formation of SNEDDS has improved the dissolution rate of Terbinafine hydrochloride.

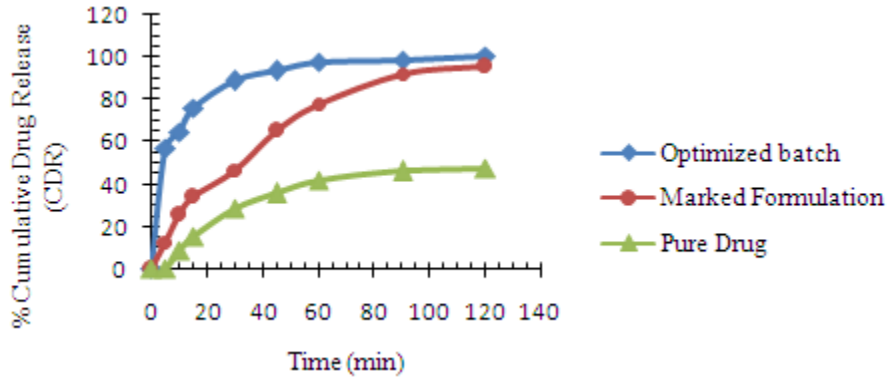

Figure 6. In-vitro drug release study of drug, marketed formulation and optimized batch of SNEDDS.

3.5.8 Drug release kinetics study

To evaluate the release kinetics of optimized formulation and compare it with marketed formulation and pure drug; mathematical models were applied. The in-vitro drug release data was fitted into various kinetic models. Data is given in Table. 5, pure drug showed Higuchi release, which indicates release of drug by diffusion in slow and steady manner. Optimized batch were best fitted in Hixon-Crowell model, which showed that there was change in surface area and particle size. Marketed formulation followed First order release which means drug release was dependant on concentration gradient. The value of n of Korsmeyer-Peppas model in pure drug and marketed formulation indicates anomalous release of drug or also called as non-Fickian diffusion. In optimized batch n value was less than 0.5 which indicates that terbinafine hydrochloride was release form the system by Quasi-Fickian diffusion.

Table 5 Drug release kinetics

	Zero order (R^2)	First order (R^2)	Hixson-Crowell (R^2)	Higuchi model (R^2)	Korsemeyer and Peppas (n)	Release order and main transport mechanism
Pure drug	0.840	0.885	0.871	0.964	0.708	Higuchi, anomalous
Optimized batch	0.499	0.915	0.926	0.762	0.237	Hixson-Crowell, Quasi Fickian diffusion
Marketed formulation	0.859	0.983	0.944	0.962	0.665	First order, anomalous

IV. CONCLUSIONS

This study concludes that self nano-emulsifying drug delivery system was developed successfully. Formulated Terbinafine hydrochloride loaded SNEDDS has improved dissolution properties than pure form of drug. This was observed from in-vitro dissolution studies and release kinetics studies. The globule size and Zeta potential of optimized batch is ideal for lymphatic uptake and also shows good stability. From in-silico study it was observed that, oral bioavailability of SNEDDS has improved. It avoids first-pass metabolism due to less transport of fraction of drug to the portal vein. Therefore, this lipid formulation has potential to enhance the dissolution properties of poorly water soluble drug Terbinafine hydrochloride and enhance the drug bioavailability. The preclinical and clinical research of optimized drug delivery system is required before commercialization.

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