wjpmr, 2024, 10(8), 131-143

SJIF Impact Factor: 6.842

WORLD JOURNAL OF PHARMACEUTICAL AND MEDICAL RESEARCH

www.wjpmr.com

Research Article

ISSN 2455-3301

WJPMR

FORMULATION DEVELOPMENT AND EVALUATION OF SOLID SELF MICROEMULSIFYING DRUG DELIVERY SYSTEM TO ENHANCE SOLUBILITY OF VORAPAXAR

[1*]Foram Contractor, [2]Kantilal Narkhede, [3]Anuradha Prajapati, [4]Sachin Narkhede and [5]Shailesh Luhar

Department of Pharmaceutics, Smt. BNB Swaminarayan Pharmacy College, Vapi, Gujarat, India.

***Corresponding Author: Foram Contractor**

Department of Pharmaceutics, Smt. BNB Swaminarayan Pharmacy College, Vapi, Gujarat, India.

Article Received on 25/05/2024 **Article Revised on 14/06/2024** **Article Accepted on 04/07/2024**

ABSTRACT

The aim of the study was to formulate and develop Solid Self Microemulsifying Drug Delivery System of Vorapaxar. Vorapaxar is a thrombin receptor antagonist. The formulation consist of Capryol 90 as oil, Tween 80 as surfactant and PEG 400 as co-surfactant. The experiment was subject to factorial design for optimization of the formulation. Based on the design, 2 factors were evaluated, each at 3 level, and experimental trials were performed at all 9 possible combinations. The Concentration of Oil (X1) and the Concentration of Smix (Tween 80: PEG 400) (X2) were chosen as the independent variables. Zeta potential, Self Emulsification time and % Transmittance were taken as the dependent variables. The results are compared with checkpoint batch. Optimized Formulation shows Particle size (90.5nm), % Transmittance 97.5%, Zeta potential (-4.1mV) and polydispersibility index (0.24).The liquid SMEDDS was converted to S-SMEDDS by using Neusilin as adsorbing agent. S-SMEDDS shows drug release (99.55%) in 50 minutes. S-SMEDDS shows better drug release than the marketed formulation. The visual evaluation showed no change in physical appearance during stability study. After stability period, the formulation was found stable with no significant change in IR study and in- vitro drug release of formulation.

KEYWORDS: Vorapaxar, Self Microemulsifying Drug Delivery System, Pseudo- ternary phase diagram.

INTRODUCTION

According to the Categorization of Biopharmaceutics, Class II and IV active drugs (APIs) show poor solubility, lower bioavailability, and lesser dissolution. In recent times, according to active drug discovery, the number of less soluble active drugs has increased, with 70% of novel formulation presenting low aqueous solubility. The low solubility and low dissolution rate in gastrointestinal liquid. Consequently, an essential is relating to active drug development has been acknowledge as being in vitro dissolution and increasing the speed of dissolving low soluble active drugs in addition to enhance their bioavailability, representing a major task for pharmaceutical experts.[1-3]

SMEDDS is isotropic mixture of drug, surfactants, co-surfactants, and oil that easily form emulsion upon mild agitation and generate a high surface area of interaction between the SMEDDS formulation and the GI fluid. Drugs having insufficient aqueous solubility having poor bioavailability, lack of dose. To solve these problem self-micro emulsifying drug delivery system is one of the most significant approach. SMEDDS is thermodynamically stable and consist of transparent emulsion. It is composed of oil, water, surfactant and co-surfactants or co-solvent. Emulsions are dispersion of macroscopic droplets having droplets size of 1-10 µm. Emulsions are of different types oil-in-water, water-in-oil or multiple emulsion. Self microemulsifying drug delivery system expand in the Gastrointestinal tract and the digestive motility of the stomach and intestine supply agitation for self-emulsification. Tiny droplets supply greater interfacial area increasing activity of pancreatic lipase to hydrolyze triglycerides and also supply greater discharge of active drug. Surfactant is used to increase the bioavailability of drug.[4-7]

Vorapaxar is an protease activated receptor 1 antagonist, which inhibit thrombin induced platelet activation used to treat atherothrombosis. It is used to treat peripheral artery diseases. Metabolized by cytochrome P450 (CYP)3 A4and CYP2J2 in the liver and has circulating metabolite is M20 (mono hydroxy metabolite) and predominant metabolite identified in excreta is M19 (amine metabolite). Having longer half life. The daily dose Zontivity tablet and film coated tablet is 2.08 mg.

Therefore, there is a need for a pharmaceutical formulation that can improve patient compliance and side effects by increasing the solubility of Vorapaxar.[8-9]

In this research, we aimed to prepare SMEDDS containing Vorapaxar for improving solubility. Based on the results of the solubility test and the pseudoternary phase diagram, the optimal SMEDDS formulations were selected and evaluated for various physico-chemical properties, such as their globule size, zeta potential, Emulsification time, Drug release, % Transmittance and stability study. In addition, the optimal SMEDDS formulation was compared with marketed formulation, because our research is the first application of a microemulsion system to Vorapaxar.

MATERIALS AND METHODS

Material

Vorapaxar was supplied by clearsynth laboratories, Hyderabad. Capryol 90 from Gattefosse, Mumbai. Kolisolv GTA from BASF, Mumbai. Captex-355 from Abitech Corporation, Mumbai. Tween 80, Tween 60, PEG 400, PEG 200, Neusilin US2, Aerosil 200 VV from SD Fines Chemicals, Mumbai.

Methods

Solubility of Vorapaxar

Solubility of Vorapaxar in various oils (Capryol 90, Kolisolv GTA, Captex-355), surfactants(tween 60, tween80, Acrysol EL-135), co-surfactant (Propylene glycol, poly ethylene glycol 400, poly ethylene glycol 200) was determined by dissolving an excess amount of Vorapaxar in 2 ml of each of selected oils, surfactant and co-surfactant in stoppered vials. The mixtures were continuously stirred using vortex mixer for 10min and kept at 37°C±0.5°C in shaker for 72 hours to attain equilibrium. The equilibrated samples were centrifuged (3000 rpm for15 mins) and supernatant was filtered through 0.45 µm membrane filter and diluted with suitable solvent. By using ultraviolet – visible (UV_VIS) spectrophotometer Drug content was quantified. [10]

Screening of surfactant

To find appropriate surfactant having good solubilising capacity, an emulsifying ability of different surfactants (tween 60,tween 80,Acrysol EL-135,) with the screened oil was investigated. 10ml of oil phase and 10ml of surfactant were weighed and vortexed for two minutes followed by warming at 40-45°C for 30 seconds. So we can obtain an isotropic mixture. 1ml of isotropic solution was diluted with 100ml double distilled water filtered through 0.45µm membrane filter. Clear emulsion was observed visually by number of flask inversion. The resulting emulsions allowed standing for 2 hours after that transmittance were observed at 650 nm. The clear emulsion with lesser number of inversions and more transmittance was selected as best surfactant. [11]

Screening of co-surfactant

In order to find appropriate co- surfactant with good solubilizing capacity, after screening of an oil emulsifying ability of different co- surfactants (Propylene glycol, poly ethylene glycol 400, polyethylene glycol 200) with the screened oil was investigated. 10 ml of oil phase and 10 ml of co-surfactant were vortexed for 2 minutes by warming at 40-45°C for 30 seconds. So we can obtain an isotropic mixture. 1ml of isotropic mixture was diluted with 100ml double distilled water filtered through 0.45µm membrane filter. Clear emulsion was observed visually by number of flask inversion. The resulting emulsions allowed standing for 2 hours after that transmittance were observed at 650 nm. The clear emulsion with lesser number of inversions and more transmittance was selected as best co-surfactant.

Construction of pseudo ternary phase diagram

Phase diagrams are constructed to obtain the proportion of components that can result in maximum microemulsion existence area. These pseudo ternary phase diagrams were constructed with oil, surfactant/ co-surfactant and water using water titration method at room temperature. The procedure consisted of preparing solutions of different ratio of surfactant to co-surfactant by weight such as 1:1, 2:1, 3:1, etc, these solutions then vortexed for 5 mins and placed at 50°C for one hour, so that an isotropic mixture was obtained. Each of these solutions were used for preparing a mixture containing oil and Smix (mixture of surfactant and co-surfactant) in the following ratios by weight, 1:9, 2:8, 3:7, 4:6, 5:5, 6:4, 7:3, 8:2, 9:1 and after preparation vortexed for 5mins followed by placing in oven at 50°C for one hour. All the mixtures were then placed at room temperature for 24 hour. Water from 5 % to 95 % of the mixtures was observed for their appearance (turbid or clear). Coarse emulsion indicate that the sample is turbid in nature, whereas clear isotropic solution indicate formation of micro emulsion. % of oil, Smix, water at which clear mixture was formed was selected and used to construct ternary phase diagram. **Prosim Software** is used to plot pseudo ternary phase diagram.[12]

Formulation of liquid SMEDDS

From the ternary phase diagram ratio of surfactant to co-surfactant was optimized. Then by varying ratio of oil to Smix, different formulations were prepared. Formulations were prepared by preparing optimized ratio of Smix first, L-SMEDDS were prepared by incorporating 2.5 mg drug into mixtures of accurately weighed quantity of Smix and oil in glass beaker. Components were mixed using a magnetic stirrer followed by vortexing using cyclomixer and heated on a water bath at 60°C to form a homogenous mixture. The L-SMEDDS were observed for homogeneity, change in color, transparency or phase separation during storage at 37±2ºC.[13]

Experimental Design: 3^2 Full Factorial Design
3^2Full Factorial Design
A 3^2 full factorial design factor was used to explore and optimize the main effects, interaction effects and quadratic effects of the formulation ingredients on the in-vitro performance of liquid SEDDS. A total of 9 experimental runs at the center were generated and evaluated by using Design-Expert software (version12.0.2.0, Stat-EaseInc., Minneapolis, U.S.A.). The purpose of the replication was to estimate experimental error and increase the precision by computing a model independent estimate of the process standard deviation. The significant response factors studied for assessing the quality of the SEDDS formulation were zeta potential (Y1) and Self emulsification time (Y2) and %Transmittance(Y3). The data obtained after the each response was fitted to quadratic polynomial model explained by the following non-linear equation $Y=\beta0+ \beta1X1 +\beta2X2+\beta12X1X2+\beta1X12+\beta2X22+E$. where Y is the response of the dependent variables; β0 to β2 are the regression coefficients; and X1, X2 are independent variables. All the three responses were optimized by using the desirability function approach by fixing the constraints in range and minimizing the zeta potential (Y1) and Self emulsification time (Y2) and %Transmittance(Y3).[14]

Contour Plot
Contour plot is a diagrammatic representation of the values of the response and it is helpful in explaining visually the relationship between independent and dependent variables. The selected model was used to plot 2 dimension contour plot using demo version of Design Expert12 software.[15]

Response Surface Plot
Response surface plot is helpful in understanding the main and the interaction effects of variables in the formulation development. The effect of level of independent variable on the response parameter can be understood from the respective response surface plot.[16]

Optimization of SMEDDS formulation using overlay plot by Design Expert software
The desirability function approach is a technique for the simultaneous determination of optimum settings of input variables that can be used to determine minimum performance levels for 1 or more responses. The desirability procedure involves two steps:

- Determine the levels of the independent variables that synchronously construct the most desirable predicted responses on the dependent variables.
- Maximize the overall desirability with respect to the controllable factors.[17]

Characterization of liquid SMEDDS
Visual assessment
Vorapaxar liquid SMEDDS was diluted with purified water (100ml) and gently stirred with magnetic stirrer. Temperature should be 37°C.[18]

Dispersibility test
The dispersability test of SMEDDS was carried out to acssess to compatibility to disperse into emulsion and the size of resulting globules to categorize the SMEDDS. It was carried by using a standard USP paddle type 2 dissolution test apparatus, formulation was added to 500ml of water at 37°C and the paddle was rotated at 50rpm. On titration with water the SMEDDS formulation forms a mixture which was of different type. Depending upon which the in vitro performance of formulation can be assessed.[19]

Determination of self-emulsification time
It was determined using dissolution apparatus. One ml of formulation was added drop wise to 500 ml distilled water at 37±0.5°C. Agitation was provided by a conventional stainless steel dissolution paddle rotating at 50 rpm. Emulsification time assessed visually.[20]

Thermodynamic stability studies
The physical stability of a lipid formulation is very important for its performance as its can be adversely affected by precipitation of drug in excipient matrix. Poor physical stability of formulation can lead to phase separation of excipients which affects bioavailability as well as therapeutic efficiency. Also the incompatibilities between formulation and shell of capsule may cause brittleness, softness, and deleted disintegration or incomplete release of drug. The following cycles was carried out for the studies.[21]

Heating cooling cycle
The selected SMEDDS dosage form was diluted with 100 times distilled water. Six cycles between cooling temperature (4°C) and heating temperature (45°C) with exposure at each temperature for not less than 48 hours were carried. That formulation, which was stable, then was subjected to centrifugation test.[22]

Centrifugation Test
The optimized SMEDDS formulations were diluted with 100 times distilled water. Which pass heating cooling cycles are centrifuged at 3500rpm for 30 mints. The formulations which does not show phase separation are taken for the freeze thaw stress test.[23]

Freeze thaw cycle
This test was performed for accelerated stability testing of Microemulsion formulation. In this study three freez thaw cycle of formulations were exposed between temperatures 21°C-25°C for each temperature cycles not more than 48 hours. The accelerated stability studies six such cycles should be run for each batch of formulation.[24]

Cloud point measurement
Dilute 1 ml of formulation with 1000 ml of water in beaker and placed on a water bath with slowlly

increasing the temperature until the formulation turned to cloudy or turbid. It gives the detail about the stability of the microemulsion at body temperature.[25]

Percentage Transmittance

It is measured at particular wavelength using UV-spectrophotometer using distilled water as blank. Stability of microemulsion formulation with respect to dilution is checkedby diluting one ml of formulation with 100ml of distilled water and measuring transmittance using U. V. Spectrophotometer. Transmittance of samples is measured at 650nm and for each sample three replicate assays are performed.[26]

Particle size distribution(PSD) and ζ-potential analysis

SMEDDS formulation was diluted 100 times with distilled water at 37 ± 0.5˚C. It is prepared by gentle agitation for 10 min using a magnetic stirrer. It was determined using, Malvern zetasizer.[27]

Stability of Vorapaxar SMEDDS

Vorapaxar SMEDDS samples were filled in glass vials with rubber stopper and then placed in Stability chambers at 25 ±0.5˚C / 60 ± 5 % RH and 40±0.5˚C / 75 ± 5 % RH for 1 months. Duplicate samples were withdrawn at 0, 15, 30 days to evaluate their physical and chemical stabilities. The physical stability was evaluated by visual inspection for physical changes (such as phase separation and drug precipitation), and a particle size analyzer was used to determine the mean particle size after dilution with water.[28]

Conversion of liquid SMEDDS into Solid SMEDDS

The solid carriers (Adsorbing agent) used for adsorption comprised of materials that provided a high surface area that provide good binding property to Liquid. The solid carriers tried include Fujicacin and colloidal silicon dioxide (Aerosil 200) and NeusilineUS2. The L-SMEDDS formulation added drop wise on 2g of adsorbing agents in porcelain dish, after that the mixture was homogenized using glass rod to confirm uniform distribution of formulation.[29]

In vitro drug release of S-SMEDDS

The in vitro drug release of prepared S-SMEDDS was assessed using United States Pharmacopoeia (USP) Dissolution Type II apparatus (Paddle type) at 37±0.5˚ C. S- SMEDDS containing 2.5 mg equivalent of drug was placed in 900ml of dissolution medium (0.1N HCl). The revolution speed of the paddle was maintained at 100rpm. At predetermined time intervals, 5 ml of dissolution medium was collected, filtered and the same volume of fresh dissolution medium was replenished to maintain the sink conditions. The samples were analyzed for the drug concentration using HPLC Instrument with same chromatographic conditions.[30]

RESULT AND DISCUSSION

Solubility in various Vehicles

The components in the formulation of SMEDDS were selected to have maximum solubility of Vorapaxar along with good miscibility with each other to produce an isotropic and stable system. Solubility of Vorapaxar in various vehicles was screened and the results are presented in Table 1. Vorapaxar had significantly higher solubility in Capryol 90 (225±1.32%) other than Kolisolv GTA, Captex-355. Among surfactant and co-surfactants, Tween 80(140±1.68%), PEG 400 (170±0.17%) showed highest solubility. Therefore, Capryol 90 were selected as oil phase, Tween 80 as surfactant and PEG 400 as co-surfactant based on solubility studies.

Table 1: Solubility Study in Various Vehicles.

Sr. No.	Solvent	Solubility(mg/mL)
1	**Capryol-90**	**225 ± 1**
2	Kolisolv GTA	115±0.70
3	Captex-355	220±0.69
5	**Tween80**	**140±1.68**
6	Tween60	40±0.70
7	Acrysol EL-135	65.1±0.9
8	PEG200	10.1± 0.78
9	Propylene Glycol	20.7±1.9
10	**PEG400**	**170±0.17**

Screening of surfactant and co-surfactant with capryol 90

The %transmittance values and number of inversions required for uniform emulsion, ofvarious dispersions are given in table 2 and 3

Table 2: Emulsification efficacy of surfactant with Capryol 90.

Sr. No.	Surfactant	% Transmittance	Number ofinversions
1	Tween60	98	12
2	Acrysol EL-135	97	9
3	**Tween80**	**99**	**7**

Table 3: Screening of co-surfactant with Capryol-90.

Sr. No.	Co-Surfactant	% Transmittance	Number of inversions
1	PEG-200	99	8
2	PropyleneGlycol	96	14
3	**PEG-400**	**99.83**	**6**

Construction of pseudo ternary phase diagram

Constructing a phase diagram is one of the primary step and makes a back bone of formation of SMEDDS. Nine different potential combinations of surfactant mixture to oil at different value 1:1, 2:1, 3:1, 1:2 were used for the phase diagram study of Vorapaxar SMEDDS. The boundary layer of O/W micro emulsion was determined in each phase diagram. The shaded part of phase diagram shows a microemulsion region. Components used for construction of pseudo ternary phase diagram for Vorapaxar are Capryol 90(oil phase), Tween 80(surfactant), PEG-400(co-surfactant) and distilled water (aqueous phase). Composition of Capryol 90, Smix (Tween80 and PEG-400) and water at each ratios (1:1, 2:1,3:1) values and pseudo ternary phase diagram at respective values shown in figure 1.

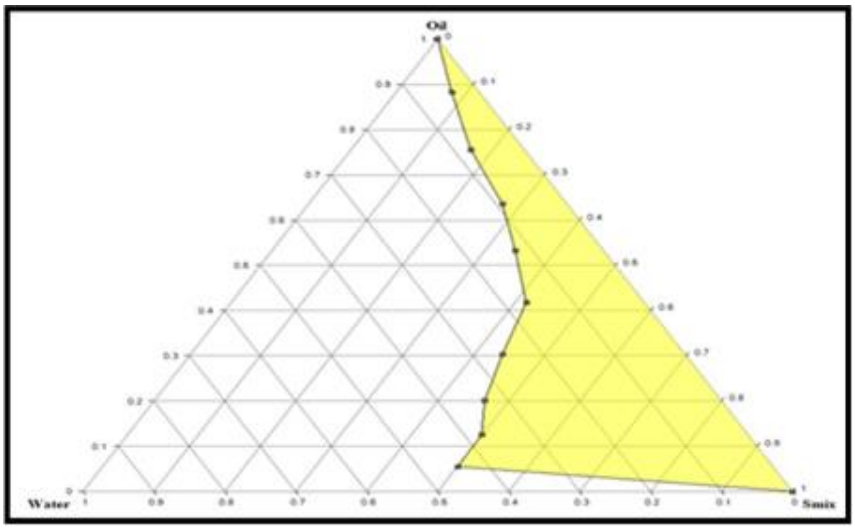

Figure 1: Pseudo Ternary Phase Diagram of Capryol90, Tween80, PEG400 andWater at 2:1.

Optimization of Formulation Using 3^2 Full Factorial Design

The 3^2 factorial design study is applied for the preparation of SMEDDS considering the factors that affect the stability as well as emulsification time.

Two independent variables selected for the study were:

- X1=Concentration of Capryol90
- X2=Concentration of Smix (2:1)Tween80+ PEG400

The responses were selected on the basis of the preliminary studies and hence it was found that the Zeta Potential, %Transmittance and Emulsification time were selected as dependent variables.

Table 4: Design matrix and response with respective observed response.

Formulation No	F1	F2	F3	F4	F5	F6	F7	F8	F9
Zeta potential(mv)	-10	-9	-8	-6	-5	-5	-3	-4	-4
PDI	0.37	0.34	0.31	0.28	0.26	0.24	0.21	0.25	0.23
Cloud point	68^0C	68^0C	68^0C	69^0C	69^0C	70^0C	70^0C	72^0C	72^0C
% Transmittance	92.8	93.5	94.2	95.7	95.5	95.8	97.1	96.9	95.6
Emulsification time (sec)	30	28	26	26	25	25	24	24	26

Table 5: Respective Response

Factorial Batches	X1 (Conc. of Capryol 90)	X2 (Conc.Of S-mix)	Y1 Zeta potential(mv)	Y2 Emulsification time(sec)	Y3 % Transmittance(%)
F1	0.15ml	0.75ml	-10	30	92.8
F2	0.2ml	0.75ml	-9	28	93.5
F3	0.25ml	0.75ml	-8	26	94.2
F4	0.15ml	0.8ml	-6	26	95.7
F5	0.2ml	0.8ml	-5	25	95.5
F6	0.25ml	0.8ml	-5	25	95.8

F7	0.15ml	0.85ml	-3	24	97.1
F8	0.2ml	0.85ml	-4	24	96.9
F9	0.25ml	0.85ml	-4	26	95.6

Table 6: Summary of Results of Multiple Regression Analysis for Y1, Y2 and Y3.

Dependent variable	Y1 Zeta potential(mv)		Y2 Emulsification time(sec)		Y3 % Transmittance (%)	
	Coefficients	P- Value	Coefficients	P-Value	Coefficients	P-Value
Intercept	-5.33	0.0027	25.00	0.0039	95.73	0.0053
X1	0.3333	0.1162	-0.5000	0.0349	0.0000	1.0000
X2	2.67	0.0004	-1.67	0.0012	1.52	0.0009
X1X2	-0.7500	0.0276	1.50	0.0029	-0.7250	0.0136
X_1^2	0.0000	1.0000	0.5000	0.1240	-0.1000	0.6453
X_2^2	-1.0000	0.0321	1.0000	0.0240	-0.6500	0.0453

Table 7: Summary of Quadratic Polynomial Equation for Responses Y1, Y2 and Y3.

Quadratic Model	Quadratic Polynomial Equation
Y1 (Zeta potential)	$-5.33+0.3333X_1+2.67X_2-0.7500X_1X_2+0.0000X_1^2-1.0000X_2^2$
Y2(Emulsification time)	$25.00-0.5000X_1-1.67X_2+1.50X_1X_2+0.5000X_1^2+1.0000X_2^2$
Y3 (%Transmittance)	$95.73+0.0000X_1+1.52X_2-0.7250X_1X_2-0.1000X_1^2-0.6500X_2^2$

Contour Plots and Response Surface Analysis

The relationship between the dependent and independent variables was further explained by constructing contour plots and 3D surface plots based on full factorial design with the help of designExpert12 software. This type of plot is used for determination of two factors simultaneously on one time.

Effect of X1 and X2 on Response Y1

Two dimensional and three dimensional plots are shown in Figure and which showed Zeta potential Decreases as the levels of Capryol90 and S-mix were Increased shown in figure 2 and 3.

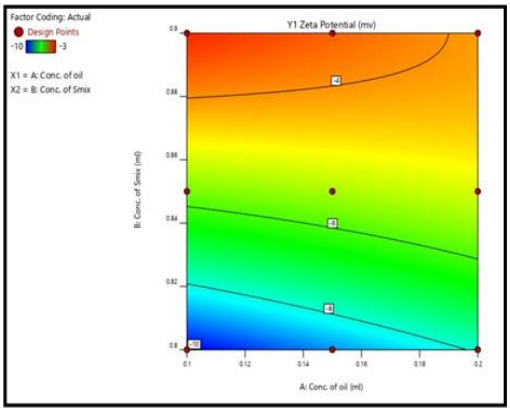

Figure 2: Contour plot for the effect of zeta potential.

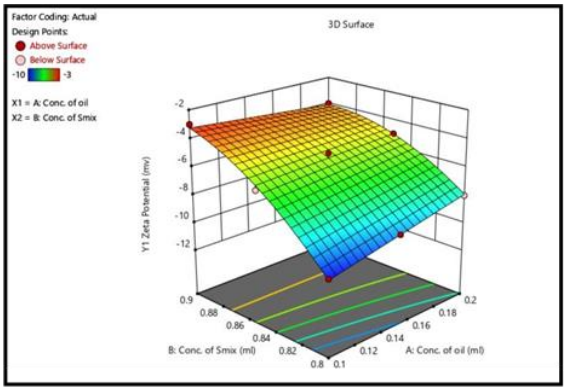

Figure 3:3 D Surface plot for the effect of zeta potential.

Effect of X1 and X2 on Response Y2

Two dimensional and three dimensional plots are shown in Figure and which showed Emulsification time Decreases as the levels of Capryol90 and S-mix were increased figure 4 and 5.

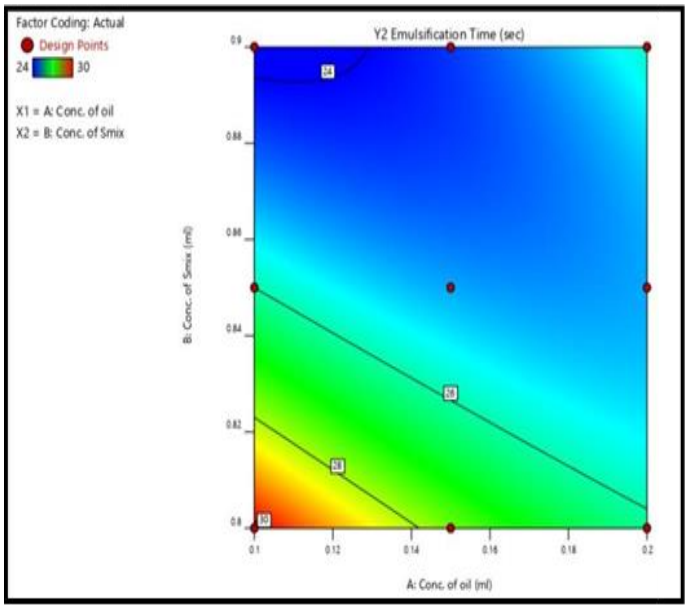

Figure 4: Contour plot for the effect of self-emulsification time.

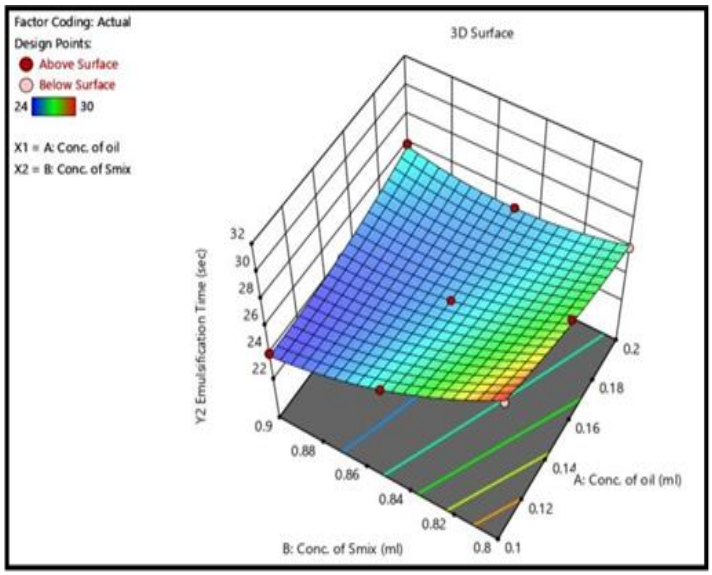

Figure 5: 3D surface plot for the effect of self-emulsification time.

Effect of X1 and X2 on Response Y3

Two dimensional and three dimensional plots are shown in Figure and which showed %Transmittance Increases as the levels of Capryol 90 and S-mix were Increased figure 6 and 7.

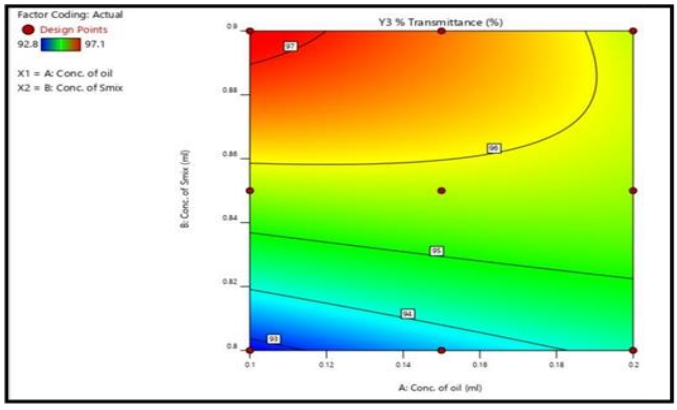

Figure 6: contour plot for the effect of % transmittance.

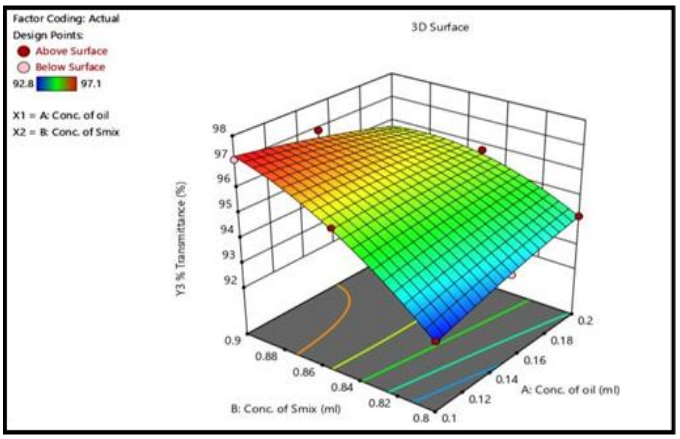

Figure 7: 3D surface plot for the effect of % transmittance.

Optimization

The optimized batch was found from the DesignExpert12. From the Contour and Response Surface Plots of the factorial batches the Overlay Plot was obtained which clearly reveals the value for X1 (conc. Of Capryol 90) and X2 (Conc. of S- mix) i.e. 0.19ml and 0.83ml respectively for the desire value of Zeta potential, Emulsification time and %Transmittance. The optimized batch was prepared as per Figure 6.38, in which yellow region is the optimized region. The formula for optimized batch was shown in figure 8.

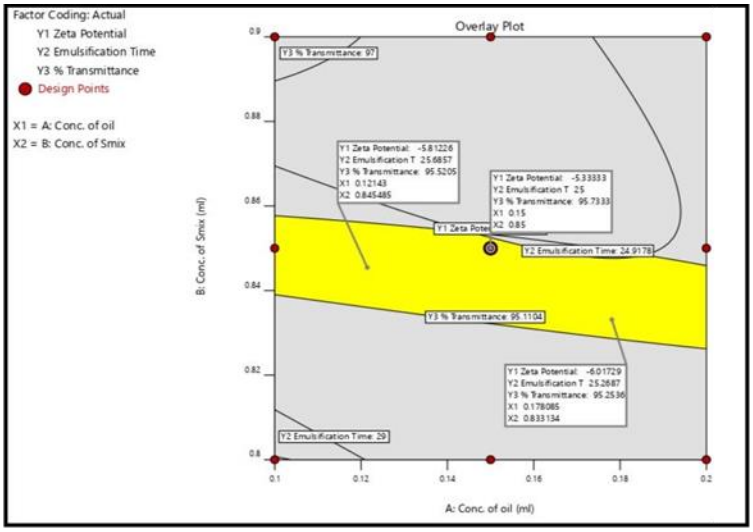

Figure 8: Overlay Plot.

Check point batch analysis

Three different check point batches (P1,P2,P3) of Vorapaxar SMEDDS were prepared according to the levels of factors as shown in Table 8. The check points was evaluated for zeta potential, self emulsification time, % Transmittance. The experimentally and theoretically computed values of zeta potential, self emulsification time, % Transmittance in Table 6.19. The results were compared using student 't' test, the difference was found to be non significant ($p<0.05$) in both cases. Ratio confirmed the utility of established contour plots and reduced polynomial equation for zeta potential, self emulsification time, %Transmittance in the preparation of SMEDDS containing Vorapaxar.

Table 8: Checkpoint batch analysis.

Batches	P1	P2	P3
X1	0.12	0.15	0.17
X2	0.84	0.85	0.83
Response	**Predicted**	**Predicted**	**Predicted**
Zeta Potential(mV)Y1	-5.8	-5.3	-6.01
Self Emulsification Time(sec)Y2	25.68	25	25.26
%TrasnmittanceY3	95.52	95.73	95.25

Table 9: Evaluation of Checkpoint Batches.

SR. NO	Parameter	Result		
		P1	P2	P3
1	Zeta potential(mv)	-5	-4.1	-4.5
2	PDI	0.26	0.24	0.23
3	Cloud point	79^0C	80^0C	80^0C
4	%Transmittance	97.4	97.5	96.27
5	Emulsification time(sec)	26.24	25.47	25.53

Characterization of optimized formulation

Globule size analysis and polydispersibility index

The Globule size of optimized L-SMEDDS of Vorapaxar was found to be 90.5 nm. The polydispersibility index was found to be 0.24. Polydispersity index of optimized formulations was found to be less than 1 which indicates that uniform distribution of globules throughout formulation. These findings indicate that, the optimized L-SMEDDS produced fine microemulsion with a small mean size and a narrow particle size distribution shown in figure 9.

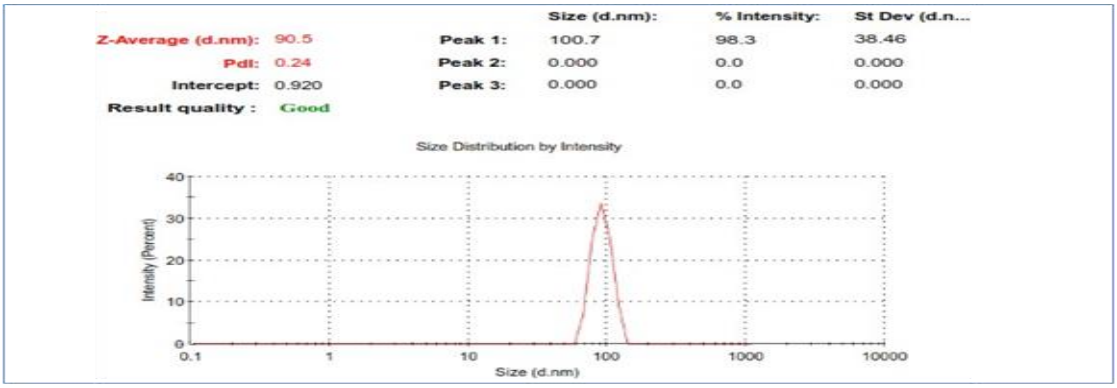

Figure 9: Globule size of optimized formulation.

Zeta Potential

Zeta Potential of optimized formulation was found to be **(-4.1 mV).** This negative zeta potential indicates greater facilation of drug permeability as well as formulation stability and hence effectiveness of the formulation. Zeta potential of optimized formula shown in figure 10.

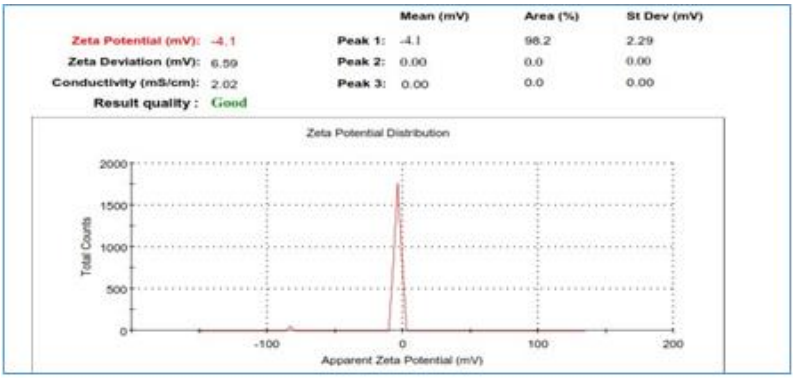

Figure 10: Zeta potential of optimized formula.

Thermodynamic Stability

Optimized L-SMEDDS Formulation which did not show any drug precipitation, phase separation after centrifugation, Heating/Cooling Cycle confirming its stable nature. Similarly, Optimized L-SMEDDS Formulation which survived freeze–thaw cycling as it was found to be reconstituted without any phase separation, drug precipitation after exposure to freeze–thaw cycling.

%Transmittance

The optimized L-SMEDDS formulation shows the percentage transmittance of around **97.5%** which is very close to 100. This implies very clear formulation, which also is an indication of the drug being completely soluble in the system. Complete drug solubility in the system is essential for the improvement of the bioavailability, which will be studied subsequently in vitro.

pH

pH of the optimized formulation was **5.9 ±0.5** indicating the acidic nature of the formulation and important for patient compliance. The mild acidic nature of the formulation is also convenient towards lesser chances of gastric irritation.

Self-Emulsification Time

Self-emulsification time of the optimized formulation was **25.47seconds.** Time less than 30 seconds indicates that the pre concentrate of Vorapaxar SMEDDS makes a homogeneous dispersion, which is a critical requirement for the in vitro dissolution.

Cloud Point

Cloud point was found to be **80℃** which indicates better stability of L-SMEDDS.

Conversion of L-SMEDDS to S-SMEDDS

L-SMEDDS were converted into S-SMEDDS by adsorption into solid carrier selection shown in table 10 and 11.

Table 10: Adsorbent Selection.

Adsorbent	Amount of Liquid SMEDDS(ml)	Amount of adsorbent required To get free flow powder(mg)mean ±SD (n=3)
Neusilin	**1**	**370±0.577**
Aerosil200	1	480±1.52
Fujicalin	1	522±2.64

Table 11: Flow properties of various adsorbent.

Adsorbent	Parameters				Inference
	Bulk density (gm/ml)	Tapped density (gm/ml)	Carr'sindex %	Hausner's ratio	
Aerosil200	0.484± 0.002	0.590± 0.001	17.96	1.21	Passable
Neusilin	**0.553± 0.002**	**0.594± 0.003**	**6.90**	**1.07**	**Excellent**
Fujicalin	0.494± 0.002	0.640± 0.001	22.8	1.29	Passable

Comparison of In-vitro Drug Release between Optimized Formulation of S- SMEDDS and Marketed Formulation

Conventional Tablet was available in the market so comparison of dissolution profile of optimized formulation and marketed preparation can be done for significance value. The drug release study was performed using Film Coated Tablet (Zontivas 2.5mg). S-SMEDDS of Vorapaxar capsule was evaluated for invitro dissolution. S-SMEDDS capsules were tested in 0.1 N Hcl for 50 minutes. S-SMEDDS release 99.55% drug in 50 minutes while marketed formulation release 55.33% drug in 50 minutes. S-SMEDDS provide better dissolution than marketed formulation.

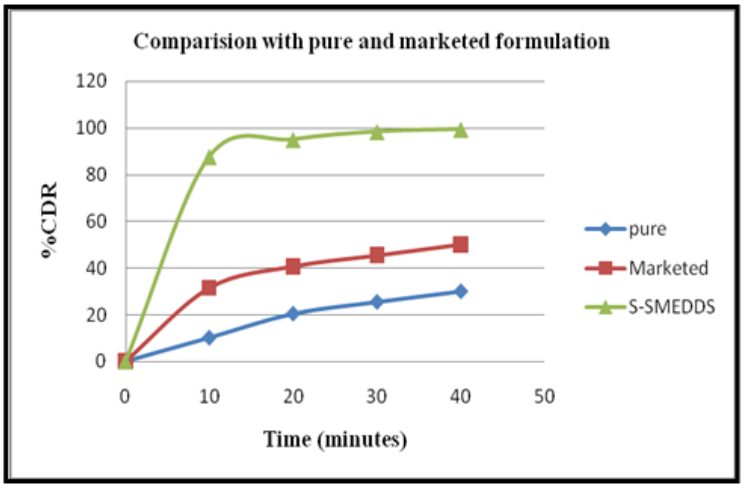

Figure 11: Comparative study of final batch.

Accelerated stability Study

- The stability study was carried out based on the ICH guideline Q2AR1.
- Storage condition was at 40°C ± 2°C / 75 ± 5% RH shown in table 12 and figure 12 and 13.

Table 12: Accelerated Stability Study.

Parameters	Accelerated Condition 40°C ± 2°C / 75 ± 5% RH		
	Initial	After 15 Days	After 30 Days
Zeta potential(mv)	-2.93	-2.87	-2.78
PDI	0.22	0.22	0.23
Cloud point	70^0C	70^0C	70^0C
% Transmittance	98.5	97.91	97.78
Emulsification time (sec)	24.47	24.25	25.11
%CDR	99.55	98.45	98.24

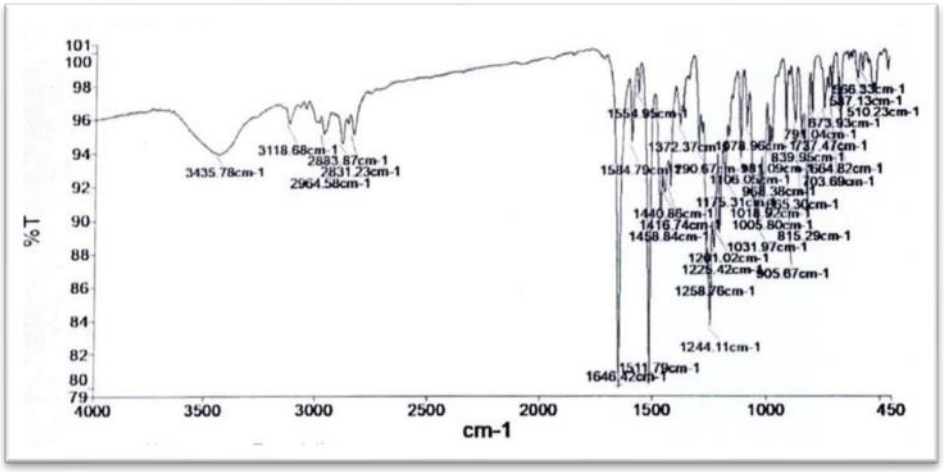

Figure 12: FTIR Spectra of Optimized Batch after Stability Study.

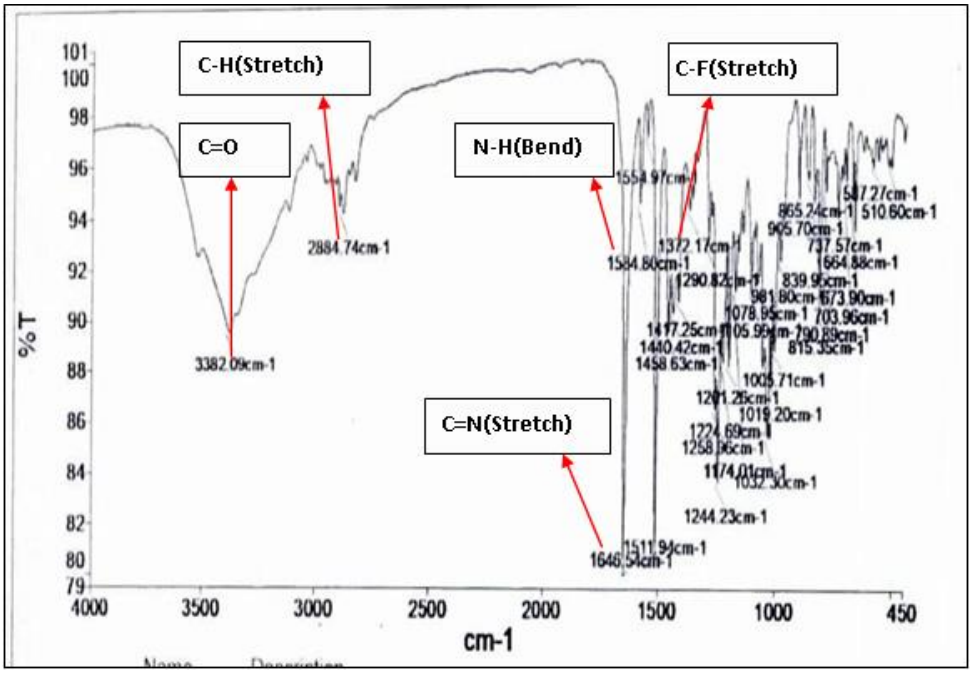

Figure 13: FTIR Spectra of Pure Drug.

CONCLUSION

Vorapaxar is a poorly water soluble drug. When administering this poorly soluble compound with hydrophilic carriers will enhance the solubility of the drug. Hence, it was concluded that Self Micro Emulsifying drug delivery system is a good approach to

enhance the solubility and dissolution property of Vorapaxar.. The composition of optimized formulation consist of Capryol 90 as oil(20%), Tween 80 (40%) as surfactant and PEG 400 (40%) as co-surfactant containing 2.5mg of Vorapaxar showing drug release for solid SMEDDS formulation (99.55%), Particle size (90.5nm), Zeta potential (-4.1) and polydispersibility index (0.24). In-vitro drug release of the optimized formulation was compared to marketed tablet. The optimized batch shows all criteria within specification, so it is concluded that Solid Self Micro Emulsifying approach was feasible at laboratory level within all the sorts of specification.

REFERENCES

1. Yujin Zhu, Jing Ye, Quan Zhang," Self-emulsifying Drug Delivery System Improve Oral Bioavailability": Role of Excipients and Physico-chemical Characterization, 2020; 8(4): 290-301.
2. R Neslihan Gursoy, Simon Benita," Self-emulsifying drug delivery systems (SEDDS) for improved oral delivery of lipophilic drugs", 2004 Apr; 58(3): 173-82.
3. Priyanka Goswami, Ananta Choudhury, Biplab Kumar Dey, "Microemulsion-a potential carrier for improved bioavailability", International Journal of Pharmaceuical & Biological Archives, 2019; 69-77.
4. Vishuajit A. Kambe, "Self microemulsifying drug delivery system", International Journal of Pharma and Bio Science, 2010.
5. U. A. DEOKATE, NITA SHINDE, UJJWALA BHINGARE, "Novel approaches for development and characterization of SMEDDS", 2013.
6. Shambhu Dokania and Amita K. Joshi, Self microemulsifying drug delivery system –challenges and road ahead, 2015.
7. Khoo SM et al "Formulation design and bioavailability assessment of zlipidic self-emulsifying formulations of halofantrine". Internationaljournal of pharmaceutics, 1998 Jun 1; 167(1-2): 155-64.
8. Drug-Bank."Vorapaxar",October-2022 https://go.drugbank.com/drugs/DB092300
9. Pubchem"vorapaxar",October,2022https://pubchem. ncbi.nlm.nih.gov/compoun d/Vorapaxar
10. HaiRong Shen and MingKang Zhong, "Preparation and evaluation of self- microemulsifying drug delivery systems (SMEDDS) containing atorvastatin", Journal of Pharmacy and Pharmacology, 2006; 58: 1183–1191.
11. Sanjib Bahadur, Kamesh Yadu," REVIEW OF FORMULATION AND EVALUATION OF SELF-MICROEMULSIFY- ING DRUG DELIVERY SYSTEM (SMEDDS)", Scientific Journal, 2020; 2519- 4852.
12. Alalor, C.A., Okafo, S.E., Onyeisi J." Formulation and Evaluation of Coconut Oil–based Diclofenac-loaded Solid Self-Emulsifying Drug Delivery System", African Journal of Biomedical Research, 2021; 24: 181- 186.
13. Bhavsar MD, Tiwari SB, Amiji MM. Formulation optimization for the nanoparticles-in-microsphere hybrid oral delivery system using factorial design. Journal of controlled release, 2006 Jan 10; 110(2): 422-30.
14. Sura Jasem Mohammed Breig, "Response surface methodology: A review on its applications and challenges in microbial cultures" 2021; 2214-7853.
15. Abhijeet S. Kunwarpuriya, "Formulation and Evaluation of Self- Microemulsifying Drug Delivery System of Fluvastatin Sodium", Journal of Pharmaceutical Science and Bioscientific Research, 2020; 10(1): 120-133.
16. Beg S, Sandhu PS, Batra RS, Khurana RK, Singh B. QbD based systematic development of novel optimized solid self nanoemulsifying drug delivery systems (SNEDDS) of lovastatin with enhanced biopharmaceutical performance. Drug delivery, 2015 Aug 18; 22(6): 765-84.
17. Sarwar Beg, Premjeet Singh Sandhu," QbD-based systematic development of novel optimized solid self-nanoemulsifying drug delivery systems (SNEDDS) of lovastatin with enhanced biopharmaceutical performance", 2014; 765-784.
18. Abhijeet S. Kunwarpuriya, "Formulation and Evaluation of Self- Microemulsifying Drug Delivery System of Fluvastatin Sodium", Journal of Pharmaceutical Science and Bioscientific Research, 2020; 10(1): 120-133.
19. Pouton CW. Lipid formulations for oral administration of drugs: non-emulsifying, self-emulsifying and 'self-microemulsifying' drug delivery systems. Eur J Pharm Sci., 2000; 11: S93–S98. doi: 10.1016/S0928-0987(00)00167-6.
20. Goyal U, Arora R, Aggarwal G. Formulation design and evaluation of a self-microemulsifying drug delivery system of lovastatin. Acta Pharm., 2012; 62: 357–70.
21. Mahajan S, Singh D, Sharma R, Singh G, Bedi N. pH-independent dissolution and enhanced oral bioavailability of aripiprazole loaded solid self-microemulsifying drug delivery system. AAPS PharmSciTech., 2021 Jan; 22: 1-8.
22. Quan G, Niu B, Singh V, Zhou Y, Wu CY, Pan X, Wu C. Supersaturable solid self-microemulsifying drug delivery system: precipitation inhibition and bioavailability enhancement. International Journal of Nanomedicine., 2017; 12: 8801
23. Macku J, Kubova K, Urbanova M, Muselik J, Franc A, Koutna G, Pavelkova M, Vetchy D, Masek J, Maskova E, Brus J. Rational Design of Self-Emulsifying Pellet Formulation of Thymol: Technology Development Guided by Molecular-Level Structure Characterization and Ex Vivo Testing. Pharmaceutics, 2022 Jul 25; 14(8): 1545.
24. Charman SA, Charman WN, Rogge MC, Wilson TD, Dutko FJ, Pouton CW. Self-emulsifying drug delivery systems: Formulation and biopharmaceutic evaluation of an investigational lipophilic compound. Pharm Res., 1992; 9: 87–93.

25. Patel PA, Chaulang GM, Akolkotkar A, Mutha SS, Hardi-kar SR and Bhosale AV. Self Emulsifying Drug Delivery Systems (SEDDS) of Nimodipine. AAPA Pharm. Sci. Tech., 2008; 9(1): 191- 96.
26. Patel D, Sawant K K. Oral Bioavailability Enhancement of Acyclovir by Self-Microemulsifying Drug Delivery Systems (SMEDDS). Drug Dev Ind Pharm., 2007; 33: 1318-26.
27. Patel AR and Vavia PR. Preparation and In vivo Evalua-tion of Self Microemulsifying Drug Delivery System (SMEDDS) Containing Fenofibrate. The AAPS Journal, 2007; 9(3): E344-E351.
28. Patil P, Patil V, Paradkar A. Formulation of Self-Emulsifying System for Oral Delivery of Simvastaitn: In vitro and in vivo evaluation. Acta Pharm., 2007; 57: 111-122.
29. Kale AA, Patravale VB. Design and Evaluation of Self-Emulsifying System for Oral Emulsifying Drug Deliv-ery System: A Review. Research. J. Pharm Tech., 2008; 1(4): 313- 323.
30. Inugala S, Eedara BB, Sunkavalli S, Dhurke R, Kandadi P, Jukanti R, Bandari S. Solid self-nanoemulsifying drug delivery system (S-SNEDDS) of darunavir for improved dissolution and oral bioavailability: in vitro and in vivo evaluation. European Journal of Pharmaceutical Sciences, 2015 Jul 10; 74.