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FORMULATION AND EVALUATION OF SELF MICRO EMULSIFYING DRUG DELIVERY SYSTEM OF POORLY WATER SOLUBLE SELEXIPAG

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ABSTRACT

Objectives- Aim of present investigation is to formulate possible lipid-based formulation of drug such as SMEDDS, SMEDDS is a isotropic mixture of oil, surfactant, and co-surfactant SMEDDS is thermodynamically stable system and required low energy method, SMEDDS can from oil in water type micro emulsion type has the potential to deliver poorly water-soluble drugs. selexipag used for treatment of pulmonary arterial hypertension (PAH) Due to poor water solubility of selexipag, however, makes it difficult to administer drugs effectively. The use of Micro emulsion systems has shown promise in improving the bioavailability and solubility of medications that are not very soluble in water.

Methods- To obtain the best possible solubilization of selexipag, the high-speed homogenizer was used to create micro emulsions using combination of oil phase (coconut oil, Capmul MCM C8, soyabean oil, corn oil, sunflower oil) and surfactant (tween-80, span-20, tween-20, span-80, Transcutol-HP) and co-surfactant (propylene glycol, ethanol, PEG-400, propanol, glycerol, Acconon MC8). The formulations were evaluated in terms of zeta potential, viscosity, particle size and in-vitro release. The stability of the Micro emulsions was evaluated in a range of storage conditions, including changes in pH.

Results- D-optimal mixture design was selected for the optimization. of 11 experiments for three factors (amount of Capmul MCM C8, tween-20, Transcutol HP). Zeta potential measurements of optimized batch confirmed the moderate stability of the Micro emulsion systems.

Conclusion- Micro emulsion becomes a great formulation for poorly water-soluble drugs by increasing their bioavailability and less side effects A particle size of 226.3 nm suggests that the micro emulsion has fine particles, which can contribute to stability, optical clarity and enhanced bioavailability if used for drug delivery. The SMEDDS formulation was found to be novel, effective, safe, stable and patient friendly. It also overcomes the drawbacks associated with drugs solubility.

Keywords: Selexipag, Micro emulsion, Poorly Water-Soluble Drugs, Pulmonary Arterial Hypertension, Drug Delivery

INTRODUCTION

Selexipag is a selective prostacyclin (IP, also called PGI2) receptor agonist. Selexipag is an orally administered drug used for PAH treatment to delay disease progression and reduce hospitalization risk. Major problem associated with Selexipag are: BCS Class –II Drug (Poor solubility and high Permeability) Short Biological half life around 0.8 -2.5 hrs. Low Bioavailability The conventional oral tablet of Selexipag shows oral BA around 49% which shows the limitation of therapy. So, in the present study oral formulation of solubilized form of Selexipag is proposed **[1]**.

Pulmonary arterial hypertension is an intractable life-threatening disease with a very poor prognosis despite many treatment options. PAH is characterized by vasospasm and vascular remodeling, resulting in right ventricular dysfunction and eventually right heart failure and death. Decreased prostacyclin (IP) production is believed to play a particular role in PAH progression **[1]**. SLX is an orally administered drug used for PAH treatment to delay disease progression and reduce hospitalization risk. It is a selective IP receptor agonist with a long half-life. The activation of the IP receptor by SLX leads to vasodilation and anti-proliferation of the vascular smooth muscle cell. The advantages of such selectivity include: minimizing off-targeting effects, to the gastrointestinal tract, and avoiding the development of tachyphylaxis **[3, 4]**.

SLX is a crystalline powder with various polymorphic forms (form I, II, III). It is a lipophilic molecule (log P is 2.2) **[1]** and practically insoluble in water (class II, according to BCS) To improve the bioavailability of selexipag numerous approaches like formulation of nanosuspension, liquid solid compact, solid dispersion have been investigated. These formulations require complex method of formation and high cost of ingredients involved **[3-4]**.

A simple technique is the Self Micro Emulsifying Drug Delivery System (SMEDDS) consisting of simple formulation method, less time of formulation and easily available cheap

excipients. Self-micro emulsifying drug delivery system (SMEDDS) has in recent times emerged as one of the most fascinating approaches to improve the solubility, dissolution and oral absorption for poorly water-soluble drugs. SMEDDS is an isotropic mixture of oil, surfactant, co-surfactant and drug substance, which can form a microemulsion under conditions of gastrointestinal fluid and gastrointestinal motility after oral administration **[3]**. The resultant microemulsion with a particle size less than 100 nm and the increasing solubility of hydrophobic drug can enhance the absorption in gastrointestinal tract **[4]**.

The objectives of present study were to design, prepare, and characterize a SMEDDS formulation of Selexipag, and evaluate its in vitro property. The solubility of selexipag was determined in various vehicles. Pseudo Ternary phase diagram was constructed to determine efficient emulsified region and the resultant formulations loaded with selexipag were optimized by a D-Optimal Mixture Design. The optimal formulation of Selexipag was further investigated for physicochemical characteristics **[3]**.

MATERIAL AND METHODS

Materials was obtained as kind gift from S.D Fine chemicals from, Ahemdabad. Selexipag was obtained as kind gift from zydus laboratory ahmedabad Tween 80, and PEG 400, oleic acid, Labrasol were purchased from, Chemdyes corporation Ahmedabad. Capmul MCM C8, Acconon, Transcutol were purchased abitech corporations, Ahemdabad.

Screening of SMEDDS Formulation Solubility Studies

Screening of microemulsion components

The solubility of selexipag was carried out to select appropriate oil (Captex 355, Linseed oil, Miglyol812N, Capmul MCM C8) Co-surfactant (Tween 80, tween 20, Span 80, Labrasol), and co-surfactant (Acrysol EL135, Transcutol, Acconon MC8) **[7]**. An excess amount of selexipag was added to fixed ml of surfactant, oil, co-surfactant and the resulting mixture was shaken on vortex mixture followed by centrifugation for 10 min at 3500 rpm. The supernatant was filtered through a membrane filter paper (0.45 µm) and the filtrate was analyzed in UV Visible spectrophotometer (UV-1700, Shimadzu) at 294 nm with suitable dilution. The surfactant or co-surfactant that showed high solubility of selexipag was used in the preparation ME containing drug Construction of Pseudo Ternary Phase Diagram **[8-9]**.

Pseudo Ternary Phase Diagram

The pseudo ternary phase diagrams were constructed using the water titration method. A series of Emulsions was prepared by varying mass ratio of oil to Smix from 9:1 to 1:9. The ratio of Tween 80 to PEG400 was

optimized by varying their mass ratio from 1:0,1:1, 2:1, 3:1, to 4:1. Each pre-concentrate mixture was titrated drop-wise with distilled water at room temperature and agitated after each drop **[12]**. The end point of the titration was taken as the point when the solution became cloudy and turbid, and the quantity of water required was recorded. The pseudo ternary phase diagram was established to delineate the area of microemulsion and boundary of phases. The pseudo ternary phase diagrams were plotted using chemix software **[16]**.

Preparation of liquid SMEDDS Formulation.

Accurately weighed selexipag was dissolved in required amount of oil and then add required quantity of Tween 80 and Transcutol HP as per decided ratio from pseudo ternary phase diagram. The contents were mixed gently with magnetic stirrer until mixture turned to clear and then formulation was equilibrated for 24 hours at 37˚C **[9]**.

Preparation of solid SMEDDS of selexipag

Adsorption on solid carrier is easy and reliable method to convert liquid SMEDDS into solid product (S-SMEDDS). (Neusilin US2) shows high adsorption capacity and so it was used. The liquid SMEDDS (0.5 ml) was added dropwise over solid absorbent in a broad petri dish. After each addition, the mixture was homogenized using glass rod to ensure uniform distribution of the components. The resultant S-SMEDDS were passed through 500 mesh to get uniform free flowing aggregates. The aggregates were stored over anhydrous calcium chloride in desiccator until further evaluation **[10]**.

Optimization of SELEXIPAG Loaded SMEDDS.

A D-Optimal Mixture Design was used to optimize the composition of SMEDDS. The design layout was generated by the trial version of Design selected as ml of oil [X1], surfactant [X2] and Cosurfactant [X3] **[19]**. The measured responses (i.e. Dependent variables) were Percentage Transmittance [Y1] and Mean Droplet size [Y2] and Poly dispersity index [Y3]. The trials were run in a randomized fashion to eliminate bias in the experiment. In order to understand the importance (criticality) of variable, analysis of variance (ANOVA) and multiple linear regression was performed **[18]**. The responses for seventeen formulations were used to fit an equation for D-optimal model which can predict the properties of all possible formulations. Graphs of these properties in the form of contour plots were constructed. Polynomial model equation was developed as the best representation of the relationship between the Percentage Transmittance, Mean Droplet size and Polydispersity Index **[20]**.

Characterization of Selexipag Loaded SMEDDS.

pH and Viscosity measurement

The pH of SMEDDS was measured by pH meter and the viscosities was measured to determine rheological properties of formulations. The viscosity of the prepared SMEDDS Batches was determined by using Brookfield LVDV-11 +Pro viscometer using a spindle in triplicate **[10]**.

Dispersibility Test:

The efficiency of dispersibility was assessed using a USP apparatus 2. Each formulation of SLP ME (1 ml) was added to 250 ml of distilled water maintained at 37 ± 0.5°C, with paddle rotating at 50 rpm for gentle agitation. The in vitro performance of the formulations was visually assessed using the grading system **[11]**.

% Transparency

Percentage transparency after dilution of SLP SMEDDS formulation with purified water (1 ml with 100 ml) was determined by UV-Visible spectrophotometer at 650 nm against distilled water as the blank **[11]**.

Cloud Point:

Prepared selexipag SMEDDS formulations were diluted by distilled water in a ratio of 1:100. The diluted samples were placed in a water bath initially at 25 °C and increased the temperature gradually. Recorded the temperature at which cloudiness occurred in a formulation **[11]**.

Globule Size and Zeta Potential:

Globule sizes and zeta potential of micro-emulsion were determined by using dynamic light scattering method using Microtac particle-size analyzer. One ml of formulation was diluted to 10 ml in a test tube and gently mixedusing a glass rod. The resultant emulsion was then subjected for particle size analysis **[18]**.

Electro conductivity study, Drug Content

The SMEDDS system contains ionic or nonionic surfactant, oil, and water. This test was performed for measurement of the electro conductive nature of system **[7]**. The electro conductivity of resultant system was measure by electro conductometer. In conventional SMEDDS, the charge on an oil droplet is negative due to presence of free fatty acids. Drug from pre-weighed SMEDDS was extract by dissolving in suitable solvent. Drug content in the solvent extract is analyse by suitable analytical method against the standard solvent solution of drug **[18]**.

In-vitro release study

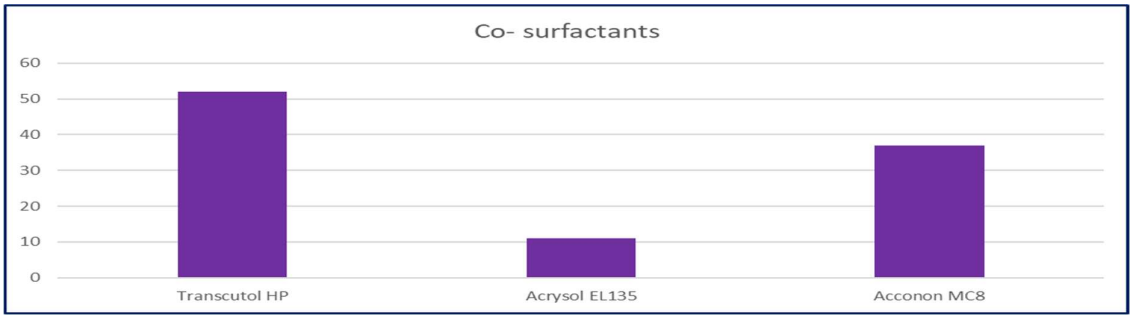
SMEDDS containing SLP were studied for drug release profile. One ml solution was put on the donor compartment. One ml solution was withdrawn from each in the time interval of 0, 10, 20, 30, 40, 50, 60, 70, 80, 90 min. The Samples were withdrawn at predetermined time intervals with fresh media replacement and analyzed by using analytical techniques **[4]**.

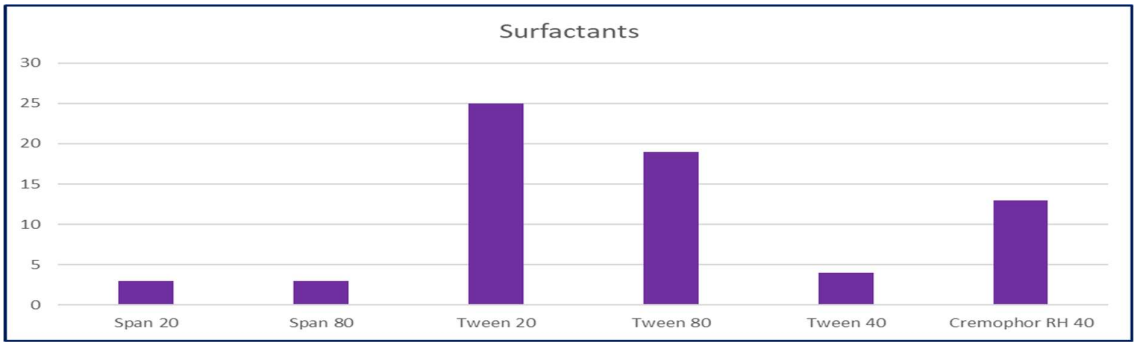
RESULT AND DISCUSSION

Screening of microemulsion components

The solubility of selexipag was carried out to select appropriate oil (Captex 355, Linseed oil, Miglyol812N) surfactant (Tween 80, tween 20, Span 80, Labrasol), and co-surfactant (Acrysol EL135, Transcutol, Acconon MC8). An excess amount of selexipag was added to fixed ml of surfactant, oil, co-surfactant and the resulting mixture was shaken on vortex mixture followed by centrifugation for 10 min at 3500 rpm. The supernatant was filtered through a membrane filter paper (0.45 µm) and the filtrate was analyzed in UV Visible spectrophotometer (UV-1700, Shimadzu) at 294 nm with suitable dilution. The surfactant or co-surfactant that showed high solubility of selexipag was used in the preparation ME containing drug. Highest solubility of selexipag found in Transcutol HP, tween 20, Capmul MCM C8.

Figure 1: Solubility of selexipag in Transcutol HP, tween 20, Capmul MCM C8





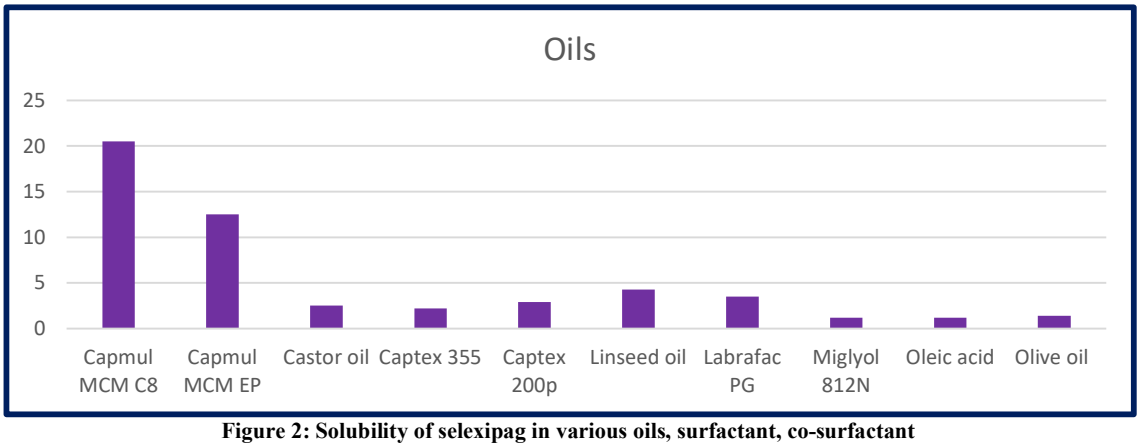


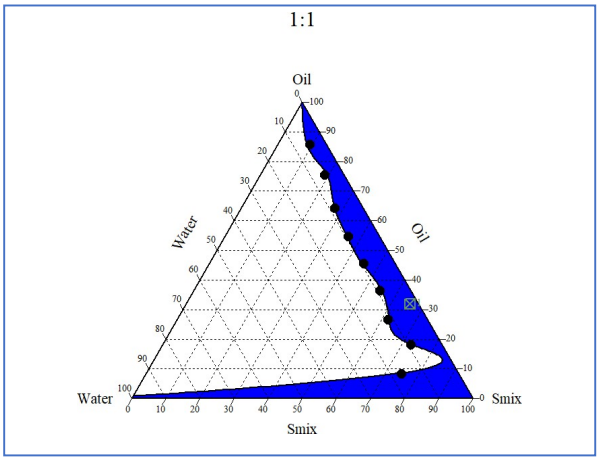
Figure 2: Solubility of selexipag in various oils, surfactant, co-surfactant

Pseudo Ternary Phase Diagram

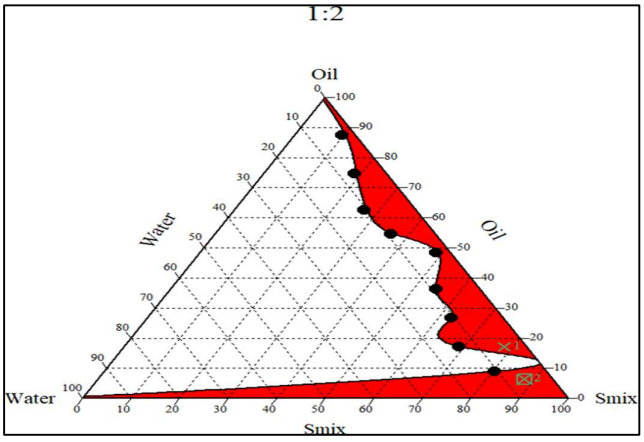
In order to obtain the appropriate concentration ranges of the components of microemulsion, the pseudo-ternary phase diagrams were constructed for different Smix ratio viz.1:1, 1:2, 2:1, 1:3 as in table. The Smix ratio which provided stable and clear microemulsions was selected for further study. With the help of phase diagram, relationship between the phase behaviour of its mixture and components could be explained. From the phase diagrams **(Figure 3)**, the largest microemulsion region was observed in Smix 2:1 ratio accordingly. The microemulsion region expanded with the increase in proportion of Capmul MCM C8 as well as Tween 20 in phase diagram of 1:2, while in the phase diagram of 1:1the microemulsion region shrunk.

Construction of pseudo ternary phase diagram;

(A)1:1



(B)1:2



(C) 2:1 (D) 1:3

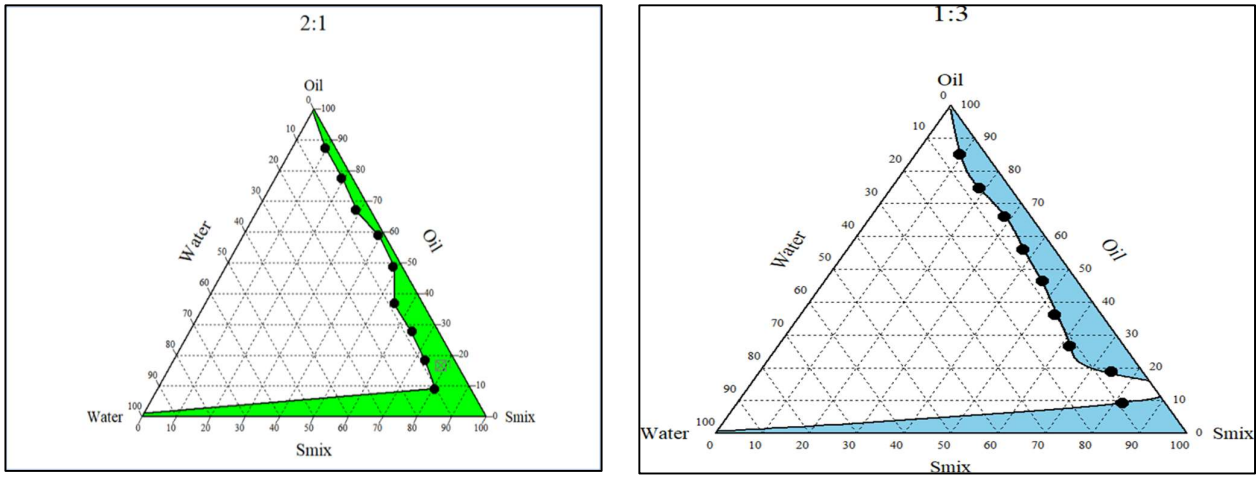


Figure 3: Pseudo Ternary Phase Diagrams containing various Smix Ratios 1:1,1:2,2:1,1:3

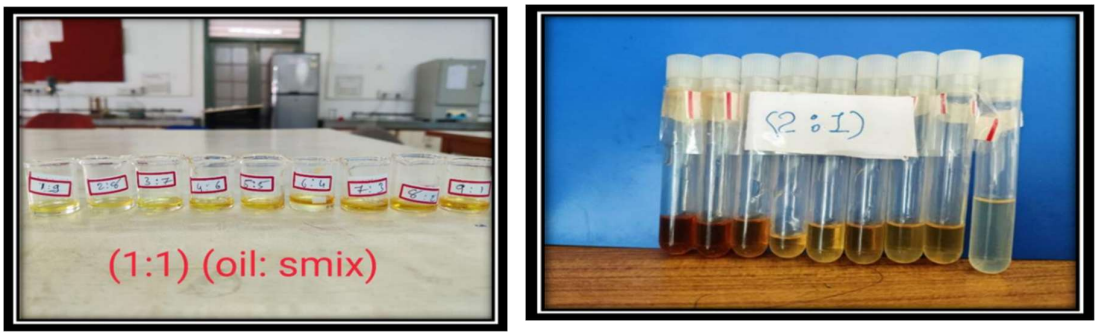


Figure 4: Oil: Smix ratio for 1:1 and 2:1

Optimization of SMEDDS by Mixture Design

Mixture design is carried out in state ease design expert 12 software. In mixture design user defined (D-optimal) design is selected for the optimization. From the pseudo-ternary phase diagram more area covered Smix ratio 2:1 is selected for optimization. In the present study, the levels of the three independent variable, Oil (X1), Surfactant (X2) and co surfactant (X3) were chosen on the basis of pseudo-ternary phase diagram. The range of components for design was selected as follow:

Table 1: Lower and higher value of factors and response of (D-optimal) design

Component	Name	Type	Minimum	Maximum
A	Oil	Mixture	3	8
B	Smix	Mixture	48	52
C	Water	Mixture	44	49

The responses (Y): Y1: Globule size (mm), Y2: Zeta Potential (mV), Y3 PDI, Y4: Drug content and Y5: Viscosity (cp) were determined after one hour of the ME

formation, in order to stabilize them. As shown in the table, Highest Globule size and Highest Zeta potential was obtained with run S2 (X1: 3%X2: 48%, X3:49%), where proportion of Smix was highest while that of oil was lowest. This is due to the increased amount of solvent necessary to solubilize the SLP in the system.

Graphical presentation of the data is easy to interpret and hence Figure were draws to results.

$Y=\beta1X1+\beta2X2+\beta3X3+\beta4X1X2+\beta5X1X3+\beta6X2X3+\beta7X1X2X3$

Where, B1, to B7 are the coefficients computed from the observed experimental values of Y. Coefficients with one factor represents the effect of that particular factor while the coefficients with more than one factor represents the interaction between those factors. Positive sign in front of the terms indicates synergistic effects while the negative sign indicates antagonistic effect of the factors.

Table 2: D-optimal mixture design with responses

Run	Batches	A:Oil	B:Smix	C:Water	Globule size nm	Zeta Potential %	PDI	Drug content	Viscosity
1	SS1	50.47	46.53	3	267.8	-30.14	0.03	94.3	0.791
2	SS2	48	49	3	226.3	-20.4	0.028	97	0.791
3	SS3	50.52	45.01	4.47	415.27	-28.32	0.032	93.6	0.876
4	SS4	48	46.45	5.55	489.21	-25.47	0.034	95.5	0.873
5	SS5	49.23	47.77	3	256.47	-26.14	0.029	91.2	0.791
6	SS6	49.24	46.44	4.31	396.1	-23.47	0.032	93.2	0.876
7	SS7	48	44	8	684.2	-28.2	0.033	9.8	0.791
8	SS8	50.04	44	5.96	411.8	-33.27	0.031	96.1	0.873
9	SS9	48	49	3	334.2	-23.14	0.045	95.8	0.791
10	SS10	52	44	4	242.2	-45.34	0.064	91.5	0.791
11	SS11	51.67	45.33	3	602.7	-42.47	0.048	89.2	0.876

Table 3: Characterization of microemulsion

Batches	%Transmittance	Emulsification time	Grade	Cloud Point Ć	pH	Conductivity	Effect of centrifugation
SS1	90.6±0.65	1.45	A	59	6.2	0.299	No phase separation
SS2	99.9±0.45	1	A	60	6.9	0.393	No phase separation
SS3	97.7±0.22	1.4	A	58	6.3	0.336	No phase separation
SS4	92.2±0.21	1.3	A	52	6.5	0.323	No phase separation
SS5	91.4±0.56	1.5	B	53	6.8	0.299	No phase separation
SS6	90.4±0.36	1.25	A	49	6.6	0.361	No phase separation
SS7	93.2±0.16	1.35	A	47	6.8	0.34	No phase separation
SS8	92.4±0.56	2.1	C	44	6.2	0.381	No phase separation
SS9	89.9±0.10	5.53	D	48	6.8	0.33	No phase separation
SS10	91.8±0.64	3.28	C	44	6.1	0.322	Phase separation
SS11	90.8±0.21	4	D	40	6.0	0.31	Phase separation

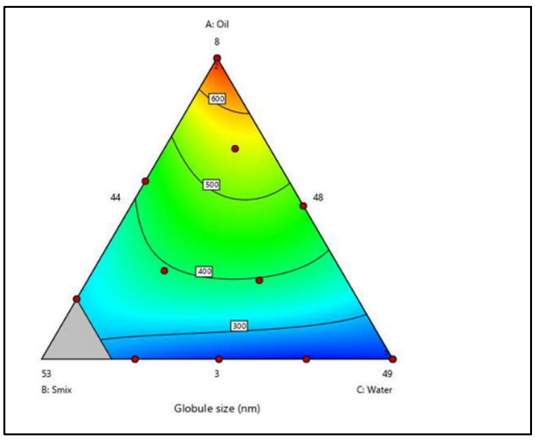
The composition of microemulsion showing lowest globule size was selected as the optimized microemulsion. The optimum composition was selected on the basis of overly contour plot. The contour plots of two responses were plotted collectively by the software to estimate an overall optimum region. The factors X1, X2 and X3 at 3.057%, 49.20% and 47.73% provided the optimum response of R1: 226.3 nm and R2: -20.4, R3:0.028, R4:97 And R5:0.79. In order to assess the reliability of the developed mathematical model, microemulsion formulation with optimized components was formed corresponding to above mentioned factor levels. Percentage prediction error (PPE) was determined as one hundredth times the ratio of difference between the experimental value and predicted value to the experimental value. The magnitudes of PPE for R1 and R2 were and respectively. The lower values of PPE (<10) indicate robustness of the mathematical model and high prognostic ability of the experimental design.

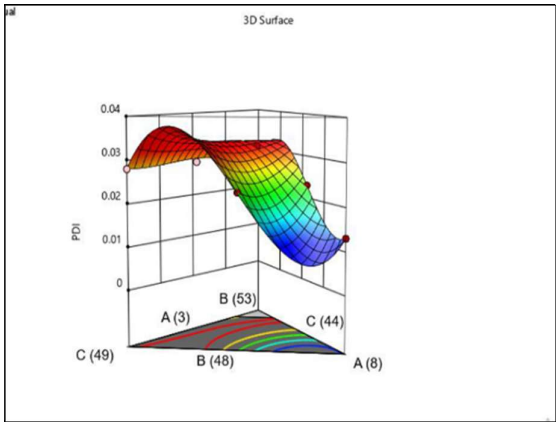
Table 4: Statistical parameters by ANOVA analysis for models and responses

RESPONSES	MODEL	SD	R^2	ADUJUSTED R^2	PREDICTED R^2
Y1	Liner	40.95	0.95	0.94	0.9273
Y2	Liner	2.95	0.8902	0.8682	0.8437
Y3	Liner	0.004	0.7643	0.7171	0.6589
Y4	Liner	2.26	0.5578	0.4693	0.1783
Y5	Liner	0.0432	0.1639	-0.0033	-0.4172

Contour plots and response surface analysis;

Two-dimensional contour plots and three-dimensional response surface plots are presented in **Figure 6 and 7**, which is useful to study the interaction effects of the factors on the responses. The relationship between the dependent and independent variables was elucidated by constructing response surface plots.





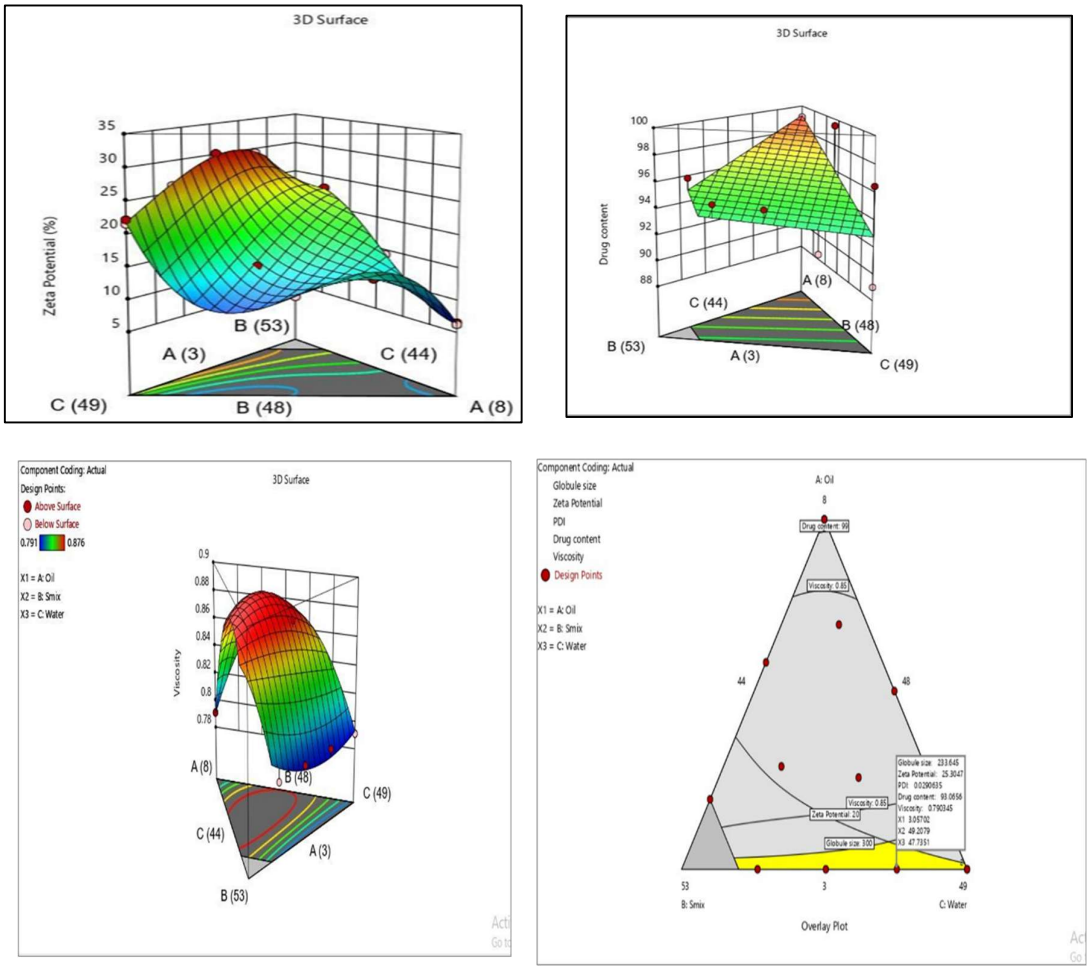


Figure 5: Contour plot and response surface plot showing the relationship between various levels of independent variables (Concentration. of oil, Surfactant and Co-surfactant) on Mean Droplet Size, PDI, Zeta potential, Drug content, viscosity

Mean Droplet size

The Mean Droplet Size of all eleven batches are presented in **Table 2**. The Mean Droplet Size ranged from 150.7-601.8 nm which indicates that all batches quickly gets converted to fine emulsion upon dilution. The selected cubic model was used to generate following equation for Mean Droplet Size.

Globule size =671.339 * A + 268.079 * B + 222.864 * C + -211.8 * AB + 169.63 * AC + 16.325 *BC

The influence of micro-emulsion components on mean droplet size is shown in contour plot **(Figure 5)**. As indicated in **Figure 6** the mean droplet size increases with the increase in oil phase and decreases with the increase in the surfactant phase. Thus we can say that increased surfactant concentration leads to formation of small droplet size globules by efficient emulsification.

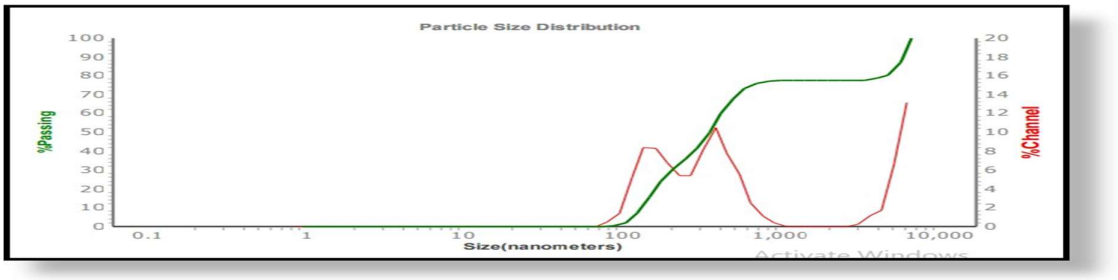


Figure 6: Mean droplet size of optimized batch

Zeta potential

The zeta potential of all eleven batches are presented in **Table 2**. The zeta potential ranged from -20 to -50 mv which indicates stability of SMEDDS The selected cubic model was used to generate following equation for. Zeta Potential =6.89754 * A + 27.4434 * B + 21.5056 * C + -0.680846 * AB + -10.392 * AC + 18.9744 * BC + -132.444 * ABC.

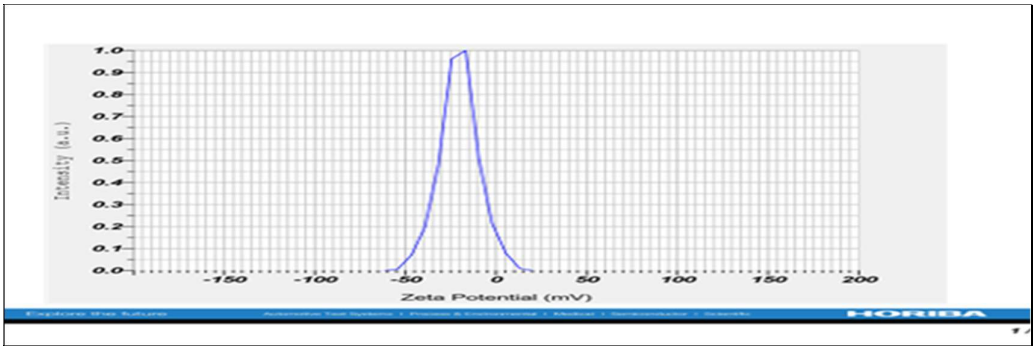


Figure 7: Zeta potential of optimized batch

Poly dispersibility index

The PDI of all eleven batches are presented in **Table 2**. Polydispersity Index ranged from 0.064-1.00 which indicates that all batches quickly gets converted to fine emulsion upon dilution. The selected cubic model was used to generate following equation for Polydispersity Index

PDI =0.0129787 * A + 0.0205489 * B + 0.0281005 * C + 0.0412259 * AB + 0.0116219 * AC + 0.0184251 * BC + 0.0303933 * ABC + -0.0692254 * AB (A-B) + -0.11298 * AC (A-C) +0.0152673 * BC (B-C)

The influence of micro-emulsion components on Polydispersity index is shown in contour plot. As indicated in **Figure 7** the poly dispersity index increases with the increase in concentration of oil and surfactant has the main effect on P.D.I as a result increase surfactant concentration leads to efficient emulsification and less P.D.I. The mean droplet size of Optimized batch of ME was found to be around 226.3

nm with polydispersity index (PDI) value of 0.028. Polydispersity is the ratio of standard deviation to the mean droplet size. This signifies the uniformity of droplet size within the formulation. The higher the value of polydispersity, the lower is the uniformity of the droplet size in the formulation.

Viscosity

The viscosity of micro emulsion systems was measured by standard rheological techniques. It depends on the batches S1-S11 was in between 0.791-0.876. From the result it was revealed that as the concentration of Surfactant increases it leads to increase in viscosity of formulation. Due to low viscosity of the formulation SMEDDS forms o/w micro emulsion water remains as external phase and viscosity of SMEDDS is near to water. The results of viscosity are as shown in **Table 2**.

Viscosity=0.79056 * A + 0.825952 * B + 0.792927 * C + 0.299219 * AB + 0.333899 * AC + -0.0854208 * BC + 0.589877 * ABC

Drug Content

The drug content of SS2 formulation was found to be 97% while other formulation drug content found less than 95% so it was concluded the batch K1 formulation have more drug content as compared to others

Drug content=99.2096 * A + 93.794 * B + 92.7361 * C.

***In vitro* release study**

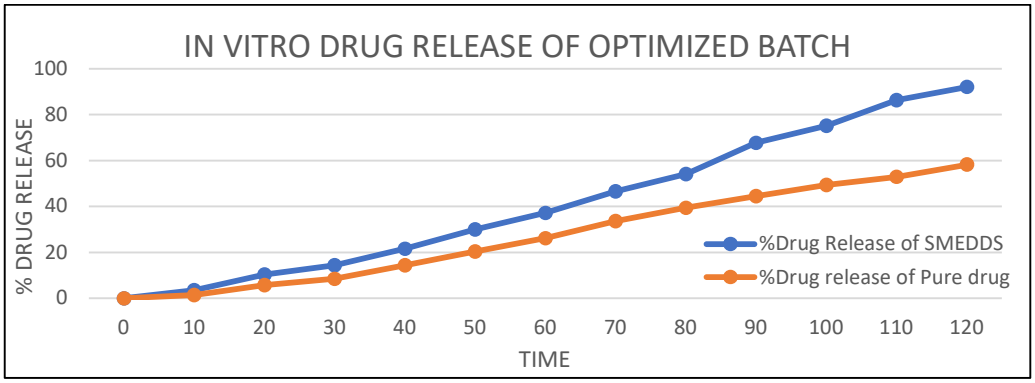


Figure 8: *In vitro* release study

In conclusion, the SMEDDS formulation of selexipag demonstrates a significantly higher release rate compared to the pure drug, indicating its potential for enhanced therapeutic performance and improved bioavailability.

Stability study:-

Stability is defined as the capacity of a drug substance or drug product to remain within established specifications to maintain its identity, strength, quality and purity throughout the retest or expiration dating periods

CONCLUSION

In the current investigation SMEDDS of selexipag was prepared and evaluated for various parameters. In the current study described the development of selexipag

SMEDDS by using water titration method. Conversion of L-SMEDDS to solid SMEDDS by using adsorbent. The main objective of this study was to enhance the aqueous solubility of selexipag. SMEDDS formulation of SLP showed better results in terms of drug content, Self emulsification time, cloud point measurements, % transmittance, zeta potential, SMEDDS, which have been shown to substantially improve oral bioavailability. The formulation was found to be novel, effective, safe, stable and patient friendly. It also overcomes the drawbacks associated with drugs solubility. If the afore mentioned formulation will scaled-up to manufacturing level, it will have increased solubility and attain higher bioavailability.

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