IJPSR (2020), Volume 11, Issue 7 (Research Article)

INTERNATIONAL JOURNAL OF PHARMACEUTICAL SCIENCES AND RESEARCH

Received on 16 March 2020; received in revised form, 23 June 2020; accepted, 26 June 2020; published 01 July 2020

FORMULATION, CHARACTERIZATION AND OPTIMIZATION OF SELF- NANOEMULSIFYING DRUG DELIVERY SYSTEM FOR WATER INSOLUBLE DRUG USING STATISTICAL DESIGN OF EXPERIMENT

R. V. Kalamkar [*1], S. J. Wadher [1] and A. S. Jain [2]

School of Pharmacy [1], SRTM University, Nanded - 431606, Maharashtra, India.
Shri D. D. Vispute College of Pharmacy & Research Center [2], Panvel - 410221, Maharashtra, India.

Keywords:

Box-Behnken design, Design of experiment, Optimization, Zaltoprofen, Self nanoemulsifying drug delivery system

Correspondence to Author:
Mr. Rajan Kalamkar

Assistant Professor,
Shri D. D. Vispute College of Pharmacy & Research Center, Panvel - 410221, Maharashtra, India.

E-mail: rajankalamkar@gmail.com

ABSTRACT: The objective of the work was to formulate a self-nanoemulsifying drug delivery system (SNEDDS) of zaltoprofen and to study the impact and interaction of various formulation variables on the formulation by the design of the experiment. A 13-run 3-factors, 3-levels box behnken design (BBD) was used for optimization with 1 replicates at the center point. The concentration of phosal 53 MCT, tween 80, and PEG 400 as oil, surfactant, and co-surfactant, respectively, were used as independent variables. Self emulsification time, % transmittance, and relative turbidity were chosen as responses for the study. Results obtained show the impact of independent variables on the response under study. The optimal concentrations of variables were found to be 27.71% (w/w) oil, 46.1% (w/w) surfactant and 19.28% (w/w) co-surfactant. The in vitro dissolution study showed a marked increase in dissolution rate than zaltoprofen powder. The box Behnken design was successfully used in the optimization of zaltoprofen SNEDDS and to study the impact of components on the response under study in a simplified and time-effective manner.

INTRODUCTION: Zaltoprofen is a newly developed NSAID having selective COX2 inhibiting activity. Zaltoprofen is used to relieve pain and inflammation after surgery and used in arthritic conditions like osteoarthritis, rheumatoid arthritis, *etc*. Further use of zaltoprofen limits because of its poor aqueous solubility and poor oral bioavailability as it belongs to BCS Class II drug. Solubility enhancement of zaltoprofen will overcome this problem, and bioavailability and therapeutic efficacy can be enhanced [1-6].

QUICK RESPONSE CODE

DOI: 10.13040/IJPSR.0975-8232.11(7).3507-16

This article can be accessed online on www.ijpsr.com

DOI link: http://dx.doi.org/10.13040/IJPSR.0975-8232.11(7).3507-16

Dissolution and bioavailability of lipophilic drugs can be enhanced by Lipid-based drug delivery systems. Self-nano emulsifying drug delivery systems (SNEDDS) is one of the approach that are used to enhance the drug dissolution by dissolving the drug in a mixture of oil, surfactant, and co-surfactant which gets disperse in small oil droplets throughout the GI tract when administered orally.

SNEDDS increases the bioavailability of drug by increasing its solubility, intestinal wall permeability and reducing the first-pass metabolism of drugs [7-10]. SNEDDS are defined as isotropic mixtures of oil, surfactant, co-solvent, and drug that rapidly form o/w microemulsion when exposed to gastric media under gentle agitation provided by gastrointestinal motion [11-13]. Different surfactants such as phospholipids, labrasol, cremophore, tween 80 can

also enhance the bioavailability of drugs by facilitating transcellular and paracellular absorption and can also act as p-glycoprotein and/ or CYP450 enzyme inhibitors, decreasing the intestinal efflux and drug biotransformation [11, 14].

As oil, surfactant, and co-surfactant use to prepare SNEDDS are liquid at room temperature, SNEDDS are viscous liquid or semisolid in nature. However, SNEDDS in the form of liquids or encapsulated in soft gelatin capsules have some limitations, especially in the manufacturing process, leading to high production costs and lower portability, inconvenient to use, and chemical incompatibility problems, leakage when capsule are used [15-17]. Therefore now a day's L-SNEDDS are converted to solid SNEDDS by various techniques such as adsorption to the solid carrier, spray drying, melt extrusion, nanoparticle technology, etc. Among these technique, adsorptions of L-SNEDDS on to inert solid carrier is the most economical and simplest technique to get free-flowing solid SMEDDS [18, 19].

DoE is used as a Quality by design (QBD) initiative to statistically study the impact of variables on critical responses under study. DoE helps to optimize the levels of variables and give the optimum combination of excipients in multi-dimensional experimental region as compare to single-variable experimentation [20-23].

The objective of the present study was to develop a stable liquid SNEDDS of water-insoluble drug zaltoprofen. Excipients were selected based on solubility and phase diagram study. Optimization of the excipients was performed by box behnken design of experimentation. Optimized zaltoprofen loaded SNEDDS was characterized for globule size analysis and *in-vitro* drug release study.

MATERIALS AND METHODS:

Materials: Zaltoprofen was obtained as a gift sample from IPCA Labs, Mumbai, Phosal 53 MCT by Lipoid, Germany, polysorbate 80 (Tween 80), and PEG 400 were purchased from Research Lab. All other chemicals were of reagent grade and used as received without further purification.

Solubility Studies: Solubility study was performed by adding an excess amount of zaltoprofen (about 100 mg) in a 2ml glass vial containing 1ml each of the selected vehicles like Oil, surfactant & Co-surfactant. This mixture was then vortex mixed and kept for equilibration for 72 h at 25 °C in orbital shaker incubator (Labline India). Then, the equilibrated samples were centrifuged using micro centrifuge (Bioera) at 10000 RPM for 15 min. Supernatant was filtered through a membrane filter (0.45 µm) and diluted with methanol for the determination of zaltoprofen.

Construction of Ternary Phase Diagram: Ternary phase diagram was constructed for the selected oil, surfactant, and co-surfactant using phosal 53 MCT, Tween 80, and PEG 400, respectively based on the results of solubility study as shown in **Fig. 1**. Ternary phase diagrams with a different surfactant to cosurfactant ratios were plotted. Surfactants and co-surfactants were used in 1:1, 2:1, and 1:2 ratios. Various formulations with different concentrations of phosal 53 MCT, tween 80, and PEG 400 were prepared. Each of the 100mg of the formulation was added to 100ml of the volumetric flask, diluted with water, and evaluated for a tendency to form a spontaneous emulsion. The extreme and middle levels of oil, surfactant, and co-surfactant were selected as independent variables for the optimization study.

Preparation of Zaltoprofen-Loaded Liquid SNEDDS: The BBD matrix for the selected independent variables is shown in **Table 1**. About 13 batches of SNEDDS were prepared by mixing the specified ratios of oil, surfactant, and cosurfactant along with the drug. The mixture was vortex mixed for about 5 min. It is characterized for self emulsification time, % transmittance, and relative turbidity. Optimized formulations were prepared by the same method.

TABLE 1: VARIABLES IN BBD

Independent Variables	Levels		
	Low (-1)	Middle (0)	High (+1)
X_1 : Amount of Oil : Phosal 53 MCT(mg)	15	30	45
X_2 : Amount of Surfactant : Tween 80 (mg)	25	50	75
X_3 : Amount of Cosurfactant : PEG 400 (mg)	10	20	30

Box–Behnken Experiment Design: A BBD with 3-factor, 3-level, 13 runs, and one replicate at the center was used to optimize the interaction effects

of the Components of liquid -SNEDDS formulation on its performance using Design-Expert software (V. 10.0.4, Stat-Ease Inc., Minneapolis, U.S.A.). Replicate at the center point was used to estimate experimental error and increase the precision.

Preliminary experiments with a ternary phase diagram containing oil, surfactant, and co-surfactant were carried out to identify the efficient region forming microemulsion. Based on these experiments, the range for each component was selected as follows: oil (15–45%), surfactant (25–75%), co-surfactant (10–30%). All the 13 experimental runs were carried out in random order. The significant response studied for optimizing the SNEDDS formulation were self emulsification time (*Y*1), % transmittance (*Y*2), and relative turbidity (Y3).

The data obtained after each response was fitted to the quadratic polynomial model, and the level of significance for the model was identified. The model fits well when the *p*-value (significance probability value) is less than 0.05, and a high level of F value at 5% significance level was obtained.

Characterization of L-SNEDDS:

% Transmittance: Zaltoprofen loaded liquid SNEDDS formulations were diluted 100 times with purified water, and its percent transmittance was measured using a UV-visible spectrophotometer at λ_{max} 638.2 nm.

Relative Turbidity: Relative turbidity of zaltoprofen loaded SNEDDS formulations were measured using digital nephaloturbidimeter by diluting the L-SNEDDS 100 times with purified water.

Determination of Self-emulsification Time: The self-emulsification time of prepared SNEDDS formulations was determined by dropwise addition of L-SNEDDS formulation to 500 mL of purified water maintained at 37 ± 0.5 °C, at 50 RPM using USP Type-II dissolution test apparatus (Lab India).

Globule Size and Polydispersity Index: The developed SNEDDS formulation diluted 100 times with purified water and analyzed for globule size of SNEDDS using Zetasizer (Malvern Instruments, UK) based on laser light scattering phenomenon.

Zeta Potential Determination: For Zeta potential measurement, the optimized L-SNEDDS diluted 100 times with purified water and zeta potential determined using a photon correlation spectrometer (Zetasizer Nano ZS 90, Malvern Instruments, UK).

Transmission Electron Microscopy: The morphology of the developed L-SNEDDS was determined using transmission electron microscopy (TEM) (Jeol/JEM 2100). A diluted liquid SNEDDS formulation was spread and observed using TEM.

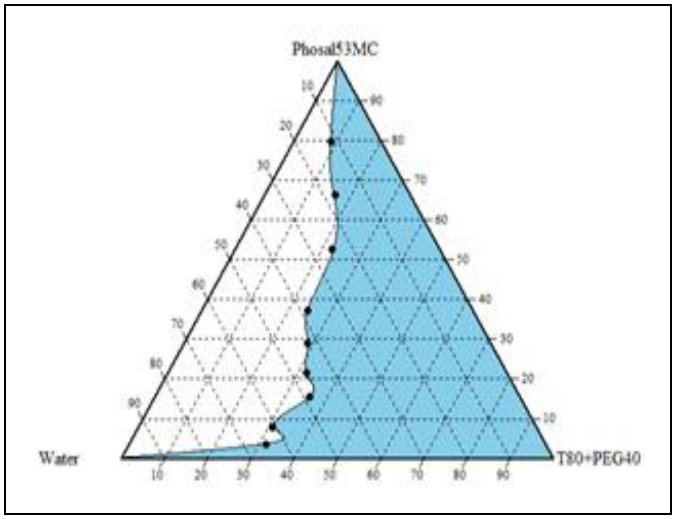
Drug Content: Prepared L-SNEDDS containing equivalent to 10 mg of zaltoprofen was added in 50 ml volumetric flask containing methanol and mixed it well with mechanical shaking and inverting volumetric flask two to three times. Then from this solution, an appropriate amount of solution was taken out and diluted appropriately with methanol and drug content for zaltoprofen was determined at 229 nm using UV- spectrophotometer.

***In-vitro* Dissolution Studies:** *In-vitro* dissolution studies for the liquid SNEDDS and pure drug each containing 80 mg of zaltoprofen was carried out using USP dissolution type-I apparatus (Lab India, Mumbai). The dissolution medium is 900 ml of 0.1M HCl, and pH 6.8 phosphate buffer maintained at 37± 0.5 ºC with basket speed of 75 rpm. At a predetermined time interval, an aliquot (five ml) of the samples were collected and replaced with fresh dissolution medium. The collected samples were suitably diluted with media, filtered through a 0.45 µm membrane filter, and analyzed for the zaltoprofen dissolved at a particular time.

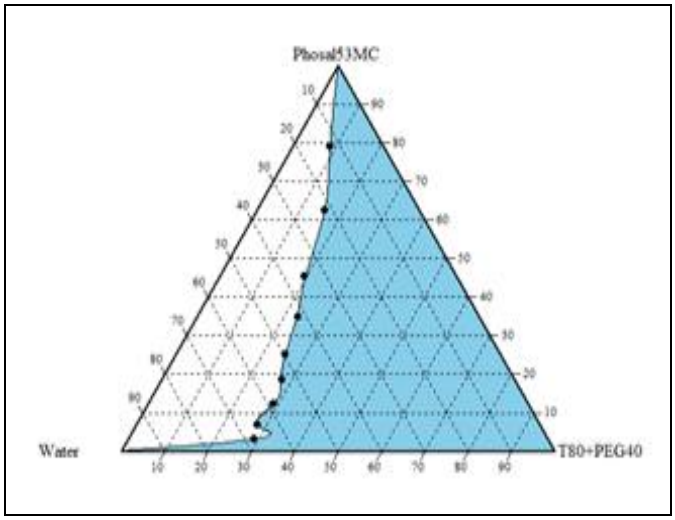
RESULTS AND DISCUSSION:

Solubility Study: The maximum amount of drug should get solubilized into the components of SNEDDS formulation and form clear and thermodynamically stable emulsion at ambient temperature when introduced to the aqueous phase. Thus, Phosal 53 MCT, tween 80, and PEG400 were chosen as an oil (X_1), surfactant (X_2), and co-surfactant (X_3), respectively as a variable for the study based on their maximum solubilization capacity. They showed a large self-emulsification domain, and solubility of zaltoprofen in this system was found to be capable of meeting the needs of the dose of the drug.

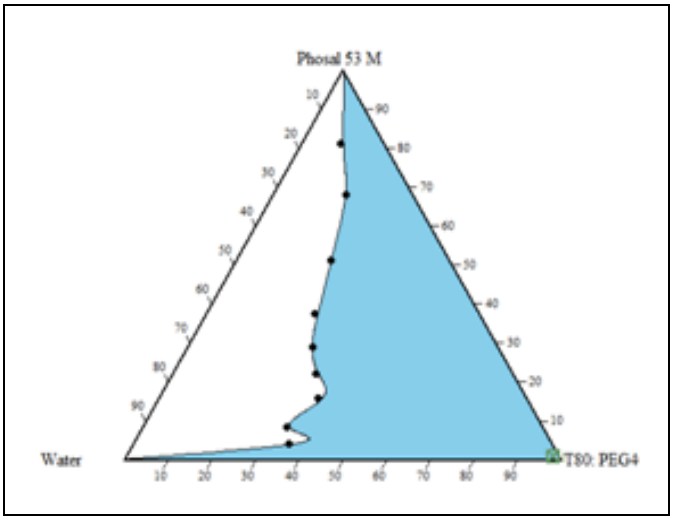
Construction of Ternary Phase Diagram: Based on the solubility of the drug in various vehicles, the ternary phase diagram was constructed for selected oils, surfactant, and cosurfactant, as shown in **Fig. 1**. It gives an optimum ratio of components in the areas forming microemulsion. A ternary phase diagram was plotted by taking phosal 53 MCT as oil phase, tween 80 as a surfactant, and PEG 400 as co-surfactant with different ratios of surfactant to cosurfactant. Ternary phase diagrams were plotted using the water titration method. The self-emulsifying region is indicated by the blue-shaded region in the diagram where there was the spontaneity of the emulsion formation, clarity of the solution, and no phase separation. From this self micro emulsifying region in the ternary diagram, the range and level for each component (independent variables) were selected as: oil (15-45%), surfactant (25-75%), co-surfactant (10-30%), as shown in **Table 1**.



Phosal 53 MCT + Tween 80 + PEG 400 (1:1)



Phosal 53 MCT + Tween 80 + PEG 400 (2:1)



Phosal 53 MCT + Tween 80 + PEG 400 (1:2)

FIG. 1: TERNARY PHASE DIAGRAM

Statistical Analysis of the Designed Experiment: A Box-Behnken experimental design with 3 factors at 3 different levels was used to study the impact of independent variables on responses under study. As per the design total, 13 formulations were prepared and characterized for responses like self emulsification time, % Transmittance, and relative turbidity, as shown in **Table 2**.

For all the 13 batches dependent variables, self emulsification time (Y_1), % Transmittance (Y_2) and relative turbidity (Y3) demonstrated wide variations from 69 to 164.9 S, 96 to 99.4% and 4.8 to 14.6 NTU respectively indicating the good influence of independent variables (X_1, X_2, and X_3) on the selected responses.

TABLE 2: BBD MATRIX AND THE OBSERVED RESPONSES

		Factor 1	Factor 2	Factor 3	Response 1	Response 2	Response 3
Std	Run	A:Oil	B: Surfactant	C:Cosurfactant	Self Emulsification Time	% Transmittance	Relative Turbidity
		Mg	Mg	Mg	Sec	%	NTU
9	1	30	25	10	158.2	97.1	9.4
13	2	30	50	20	78.4	98.2	6.1
3	3	15	75	20	69	99.4	4.8
4	4	45	75	20	132.1	97.8	9.54
8	5	45	50	30	148.3	96.2	12.2
2	6	45	25	20	164.9	96	14.6
11	7	30	25	30	127.6	96.8	10
1	8	15	25	20	99.2	98.7	5.8
5	9	15	50	10	76	99.2	5.1
7	10	15	50	30	74	98.9	5.2
10	11	30	75	10	94.1	98.8	5.2
6	12	45	50	10	150.2	97.2	11.2
12	13	30	75	30	98.2	98.6	5.4

The response surface plots shown in **Fig. 2** demonstrate the relationship between the dependent and independent variables. The mathematical relationships were established, and coefficients of second-order polynomial equation generated using multilinear regression analysis for self emulsification time, % Transmittance, and relative turbidity. The equations were found to be linear in nature with interaction terms. The coefficients of the polynomials fitted well to the data, with the values of R^2, 0.9845, 0.9858, and 0.9925 for Y_1, Y_2, and Y_3, respectively.

$$Y = \beta_0 + \beta_1X_1 + \beta_2X_2 + \beta_3X_3 + \beta_4X_1X_2 + \beta_5X_2X_3 + \beta_6X_1X_3 + \beta_7(X_1)^2 X_{12} + \beta_8 (X_2)^2 X_{13} + \beta_9(X_3)^2 X_{23} + E$$

Where, *Y* is the response of the dependent variables; β_0–β_9 are the regression coefficients; and X_1, X_2, X_3 are independent variables.

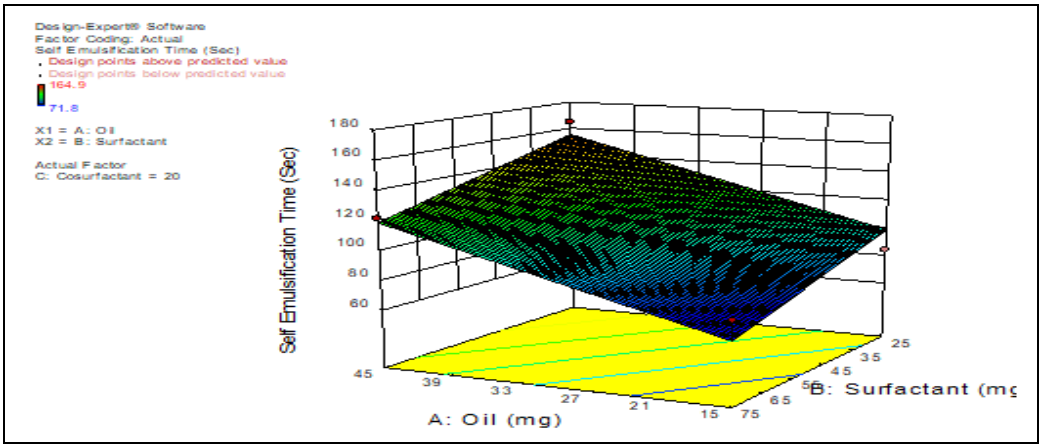
Fig. 2 shows the response surface plot, characterizing increase in the Self emulsification time and relative turbidity with an increase in the concentration of oil (Phosal 53 MCT) and decrease in the concentration of surfactant (Tween 80) whereas Increase in % Transmittance with an increase in surfactant and decrease in oil concentration. All the response surfaces were fitted with quadratic polynomial models. The ANOVA results are shown in **Table 3**.

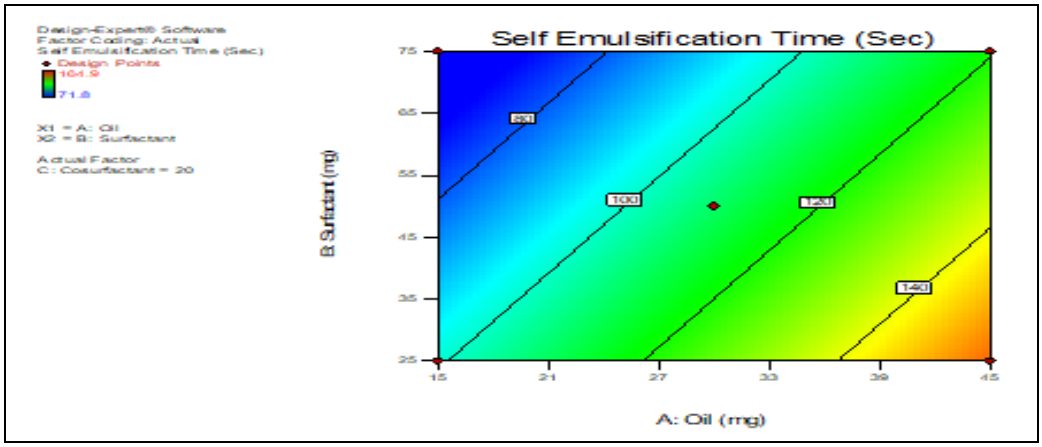
Using software optimization process and overlay plot from the software, the level selected for X_1, X_2 and X_3 were 27.71, 46.1, and 19.28 respectively, which gives theoretical values of 77.51 sec, 98.26% and 5.90 NTU for self emulsification time, % transmittance and Relative turbidity respectively. The fresh formulation was prepared using the optimum levels of independent variables.

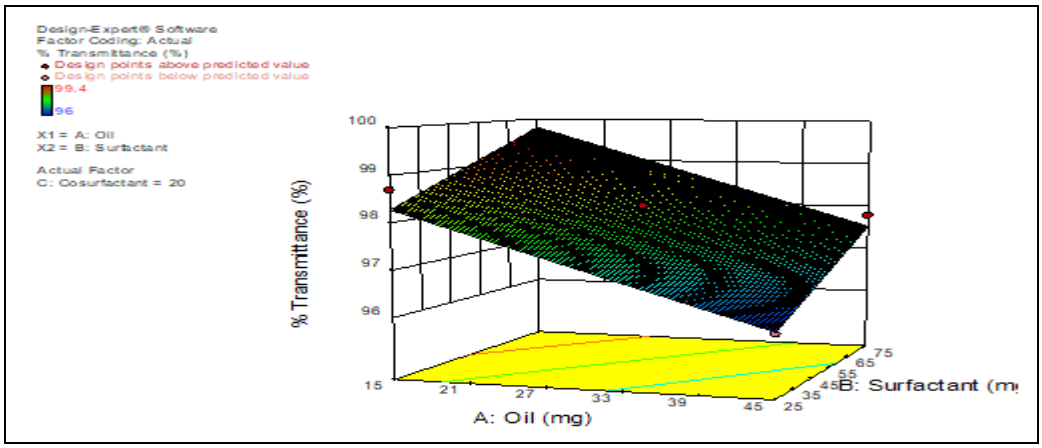
The observed values of self emulsification time, % transmittance, and Relative turbidity were found to be 75.68 sec, 98.2%, and 5.81 NTU respectively, which were in close agreement with the theoretical values.

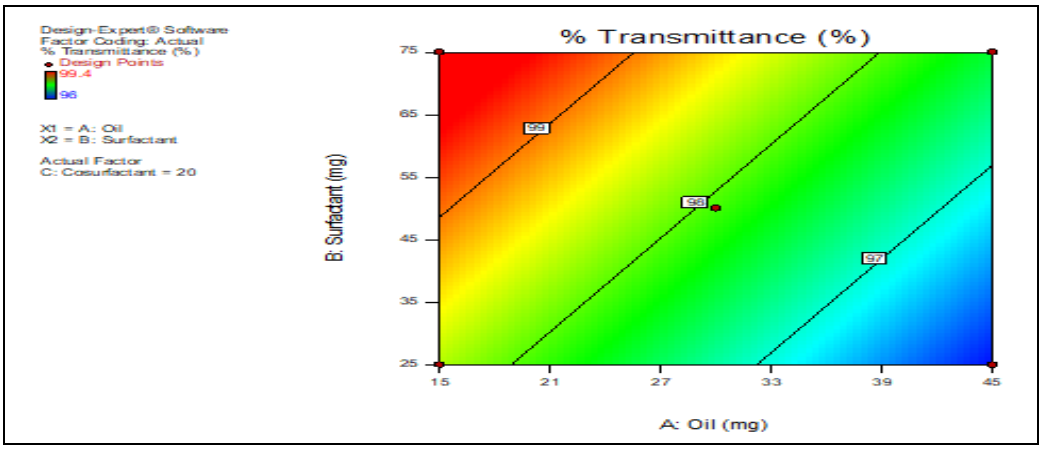
TABLE 3: RESULTS OF ANOVA

	Self Emulsification time					% Transmittance					Relative turbidity				
Source	Sum of Squares	df	Mean Square	F Value	p-value Prob > F	Sum of Squares	df	Mean Square	F Value	p-value Prob >F	Sum of Squares	df	Mean Square	F Value	p-value Prob > F
Model	14505.65	9	1611.73	21.14	0.0145	15.591	9	1.7324	23.09	0.012	128.31	9	14.257	43.91	0.0049
A-Oil	9611.911	1	9611.91	126.11	0.00151	10.125	1	10.125	135	0.0013	88.71	1	88.711	273.2	0.00048
B-Surfactant	3061.531	1	3061.53	40.17	0.00794	4.5	1	4.5	60	0.0044	27.60	1	27.602	85.02	0.00269
C-Cosurfactant	115.52	1	115.52	1.51	0.3059	0.405	1	0.405	5.4	0.1027	0.451	1	0.4512	1.390	0.32339
AB	1.69	1	1.69	0.022	0.8910	0.3025	1	0.3025	4.033	0.1382	4.120	1	4.1209	12.69	0.03774
AC	0.0025	1	0.0025	3.28	0.9957	0.1225	1	0.1225	1.633	0.2911	0.202	1	0.2025	0.623	0.48731
BC	301.0225	1	301.022	3.94	0.1410	0.0025	1	0.0025	0.033	0.8667	0.04	1	0.04	0.123	0.74877
A^2	531.5714	1	531.57	6.97	0.0775	0.0175	1	0.0175	0.233	0.6621	7.0400	1	7.040	21.68	0.01868
B^2	1172.623	1	1172.62	15.38	0.0294	0.0432	1	0.0432	0.576	0.5030	1.5746	1	1.5746	4.850	0.11491
C^2	780.1729	1	780.17	10.23	0.0493	0.1289	1	0.1289	1.719	0.2811	0.7426	1	0.7426	2.287	0.22761
Residual	228.6375	3	76.21			0.225	3	0.075			0.9739	3	0.3246		
Cor Total	14734.29	12				15.816	12				129.28	12			


Design-Expert® Software
Factor Coding: Actual
Self Emulsification Time (Sec)
Design points above predicted value
Design points below predicted value
164.9
71.8
X1 = A: Oil
X2 = B: Surfactant
Actual Factor
C: Cosurfactant = 20
Self Emulsification Time (Sec)
A: Oil (mg)
B: Surfactant (mg


Design-Expert® Software
Factor Coding: Actual
Self Emulsification Time (Sec)
Design Points
164.9
71.8
X1 = A: Oil
X2 = B: Surfactant
Actual Factor
C: Cosurfactant = 20
Self Emulsification Time (Sec)
B: Surfactant (mg)
A: Oil (mg)
84
100
120
140


Design-Expert® Software
Factor Coding: Actual
% Transmittance (%)
Design points above predicted value
Design points below predicted value
99.4
96
X1 = A: Oil
X2 = B: Surfactant
Actual Factor
C: Cosurfactant = 20
% Transmittance (%)
A: Oil (mg)
B: Surfactant (mg


Design-Expert® Software
Factor Coding: Actual
% Transmittance (%)
Design Points
99.4
96
X1 = A: Oil
X2 = B: Surfactant
Actual Factor
C: Cosurfactant = 20
% Transmittance (%)
B: Surfactant (mg)
A: Oil (mg)
99
98
97

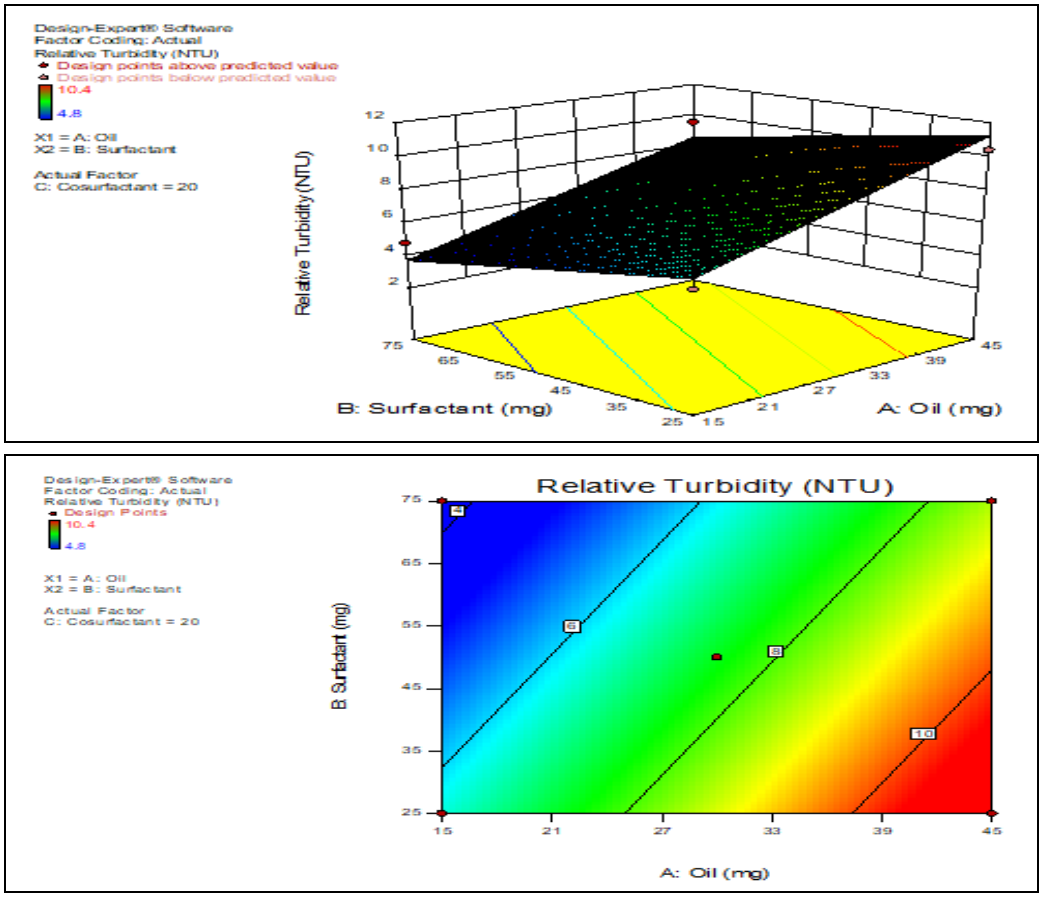


FIG. 2: 3D PLOT AND SURFACE PLOT FOR SELF EMULSIFICATION TIME, % TRANSMITTANCE AND RELATIVE TURBIDITY

Characterization of L-SNEDDS:

% Transmittance: A formulation having a high value of transmittance indicates optical clarity of formulation. The Optimized L-SNEDDS formulations showed % transmittance values above 99%, confirming the system formed is clear, transparent, and efficient for forming microemulsion.

Relative Turbidity: Low value of turbidity indicates good optical clarity. For optimized L-SNEDDS, relative turbidity was found to be 5.81± 0.1 NTU confirming the transparency of formed microemulsion.

Determination of Self-emulsification Time: Emulsion efficiency is importantly evaluated by its self emulsification time. When L-SNEDDS is added to aqueous media, under mild agitation, it should spontaneously form a microemulsion. Evaluated SNEDDS formulations exhibit good emulsification within 120 s.

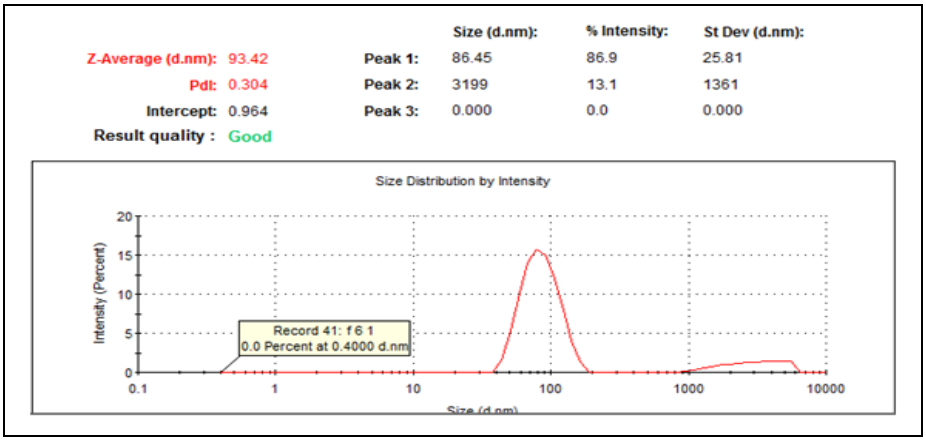


FIG. 3: GLOBULE SIZE OF OPTIMIZED L-SNEDDS

Globule Size and Zeta Potential: Globule size of a formed microemulsion is a decisive factor in self-emulsifying formulations as it determines the rate and extent of drug release and absorption. For developed, optimized L- SNEDDS formulation globule size and PDI was found to be 93.42 nm, 0.304, respectively **Fig. 3**.

Zeta potential determination of optimized L-SNEDDS: Zeta potential indicates the stability of the formed microemulsion. The presence of zeta potential to the tune of -24.4 mV on the globules conferred physical stability to the system. Observed zeta potential of optimized L-SNEDDS formulation is shown in **Fig. 4**.

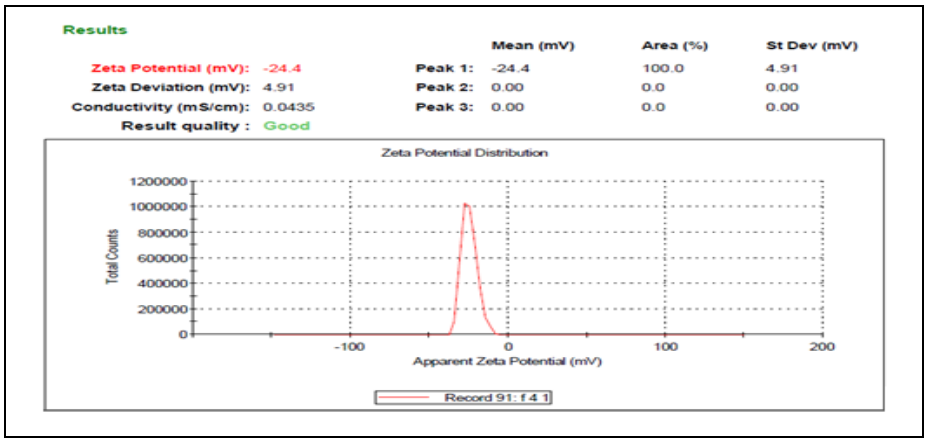


FIG. 4: ZETA POTENTIAL OF OPTIMIZED L-SNEDDS OF ZALTOPROFEN

Transmission Electron Microscopy: External morphology of L-SNEDDS was performed by TEM analysis as shown in **Fig. 5**. The TEM images show dispersed oil globules appear to be spherical with a dark background.

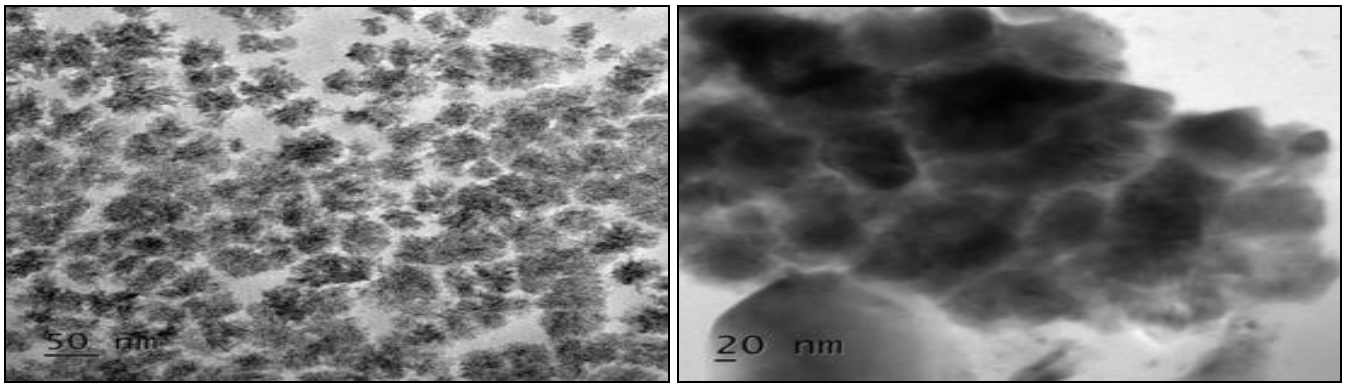


FIG. 5: TEM OF ZALTOPROFEN SNEDDS

***In-vitro* Dissolution Studies:** The dissolution profile of Zaltoprofen from L-SNEDDS in 0.1 M HCl pH 1.2 and phosphate buffer pH 6.8 was compared with the drug powder **Fig. 6**.

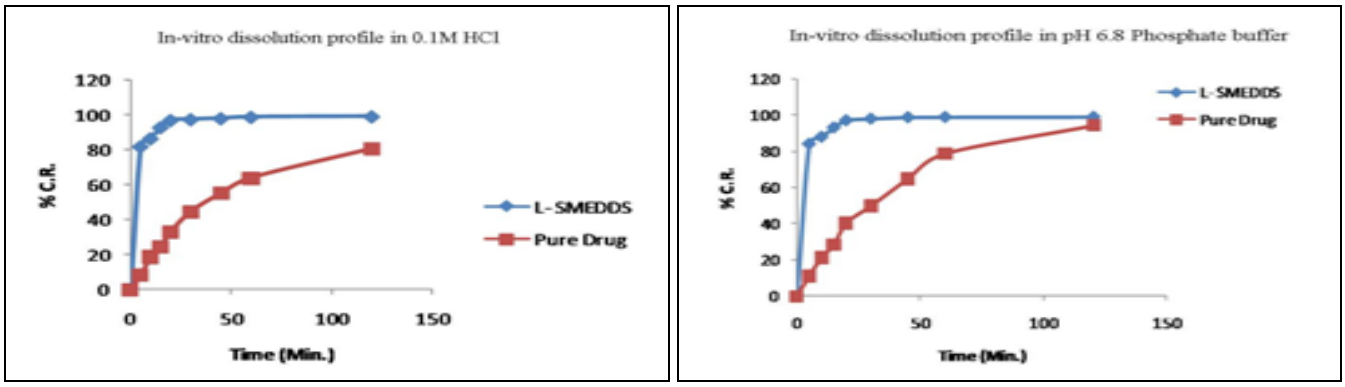


FIG. 6: *IN-VITRO* DISSOLUTION PROFILE

L-SNEDDS released more than 90% of the drug in 20 min in both 0.1 M HCl pH 1.2 and phosphate buffer pH 6.8 media, while the pure drug showed only 33.19% and 40.36% dissolution respectively. It was observed that changes in the dissolution medium had no effect on the drug release from L-SNEDDS formulation, whereas with pure Zaltoprofen, the dissolution was faster in Phosphate buffer pH 6.8 as compared to that in 0.1M HCl. The L-SNEDDS gave dissolution above 90% in 20 min without pH influence and was significantly higher than the pure drug. Thus, L-SEDDS was useful for improving the dissolution rate of the poorly water-soluble zaltoprofen.

CONCLUSION: SNEDDS formulation of zaltoprofen using phosal 53 MCT, tween 80, and PEG 400 as oil, surfactant, and co-surfactant respectively was successfully developed. The design of the experiment by box Behnken design was successfully used and shown the interaction effect of various independent variables on the response under study. *In vitro* dissolution study demonstrated that the drug dissolution rate was efficiently enhanced with developed L-SNEDDS formulation as compared to pure drug. The results of this study suggest the potential use of developed L-SNEDDS formulation for the delivery of poorly water-soluble drug zaltoprofen.

ACKNOWLEDGEMENT: We are thankful to Shri D. D. Vispute College of Pharmacy & Research Center, Panvel, and School of Pharmacy SRTMU Nanded for providing the necessary research facilities to carry out this work.

CONFLICTS OF INTEREST: The authors confirm no conflict of interest for this manuscript.

REFERENCES:

1. Ito A and Mori Y: Effect of a novel anti- inflammatory drug, 2- (10,11-dihydro-10oxo-dibenzo [b,f]-thiepin-2-yl) propionic acid (CN-100), on the proteoglycan biosynthesis in articular chondrocytes and prostaglandin E2 production in synovial fibroblasts. Res Commun Chem Pathol Pharmacol 1990; 70: 131-42.
2. Thakur S, Riyaz B, Patil A, Kaur A, Kapoor B and Mishra V: Novel drug delivery systems for NSAIDs in management of rheumatoid arthritis: An overview. Biomed Pharmacother 2018; 106: 1011-23.
3. Japanese Pharmacopoeia, Ministry of health, labour and welfare 2011: 1435-36.
4. Chatap V, Marathe G and Maurya A: Formulation and Evaluation of Zaltoprofen Fast Disintegrating Tablet. Journal of Pharma Sci Tech 2013; 3(1): 20-26.
5. Kiran HC, Dhandapani NV and Raman RK: Formulation and characterisation of sustained release microbeads loaded with zaltoprofen. Int J App Pharm 2019; 11(5): 173-80.
6. Londhe V and Save S: Zaltoprofen loaded solid lipid nanoparticles for topical delivery: formulation design, *in-vitro* and *ex-vivo* evaluation. MOJ Bioequiv Availab. 2017; 4(2): 248-54.
7. Beloqui A, Pozo-Rodríguez A, Isla A, Rodríguez-Gascón A and Solinís MA: Nanostructured lipid carriers as oral delivery systems for poorly soluble Drugs. Journal of Drug Delivery Science and Technology 2017; 42: 144-54.
8. Göke K, Lorenz T, Repanas A, Schneider F, Steiner D, Baumann K, Bunjes H, Dietzel A, Finke JH, Glasmacher B and Kwade A: Novel strategies for the formulation and processing of poorly water-soluble drugs. Eur J Pharm Biopharm 2018; 126: 40-56.
9. Tung NT, Tran CS, Pham TM, Nguyen HA, Nguyen TL, Chi SC, Nguyen DD and Bui TB: Development of solidified self-microemulsifying drug delivery systems containing l-tetrahydropalmatine: Design of experiment approach and bioavailability comparison. Int J Pharm 2018; 537(1-2): 9-21.
10. Saipin S, Sirima M and Narubodee P: Development and evaluation of self-microemulsifying liquid and pellet formulations of curcumin, and absorption studies in rats. Eur J Pharm Biopharm 2010; 76: 475-85.
11. Elnaggar Y, El-Massik M and Abdallah O: Self-nanoemulsifying drug delivery systems of tamoxifen citrate: Design and optimization. Int J Pharm 2009; 380: 133-41.
12. Prajapat MD, Patel NJ, Bariya A, Patel SS and Butani SB: Formulation and evaluation of self-emulsifying drug delivery system for nimodipine, a BCS class II drug. Journal of Drug Delivery Science and Technology 2017; 39: 59-68.
13. Date AA and Nagarsenker MS: Design and evaluation of self nanoemulsifying drug delivery systems (SNEDDS) for cefpodoxime proxetil. Int J Pharm 2017; 329: 166-72.
14. Basalious E, Shawky N and Badr-Eldin S: SNEDDS containing bioenhancers for improvement of dissolution and oral absorption of lacidipine I: Development and optimization. Int J Pharm 2010; 391: 203-11.
15. Gadhave RJ and Tarkase KN: Formulation and evaluation of novel lipid based solid-self nanoemulsifying drug delivery system of agomelatine 2018; 7(6): 1203-24.
16. Spandana I, Basanth B and Sharath 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.
17. Huo T, Tao C, Zhang M, Liu Q, Lin B, Liu Z, Zhang J, Zhang M, Yang H, Wu J, Sun X, Zhang Q and Song H: Preparation and comparison of tacrolimus-loaded solid dispersion and self-microemulsifying drug delivery system by *in-vitro/in-vivo* evaluation. Eur J Pharm Sci 2018; 114: 74-83.
18. Garg V, Kaur P, Singh SK, Kumar B, Bawa P, Gulati M and Yadav AK: Solid self-nanoemulsifying drug delivery systems for oral delivery of polypeptide-k: Formulation, optimization, *in-vitro* and *in-vivo* antidiabetic evaluation. Eur J Pharm Sci 2017; 109: 297-315.
19. Tung NT, Tran CS, Pham TM, Nguyen HA, Nguyen TL, Chi SC, Nguyen DD and Bui TB: Development of solidified self-microemulsifying drug delivery systems containing l-tetrahydropalmatine: Design of experiment

approach and bioavailability comparison. Int J Pharm 2018; 537(1-2): 9-21.
20. Yadav P, Rastogi V and Verma A: Application of Box-Behnken design and desirability function in the development and optimization of self-nanoemulsifying drug delivery system for enhanced dissolution of ezetimibe. Future J. Pharm Sci 2020; 6: 7.
21. Luis A, Susana L, Ellen C, Priscila B, Felipe T, Luís A, Stephania F, Marcilio S and Ricardo N: Preparation of a solid self-microemulsifying drug delivery system by hot-melt extrusion. Int J Pharm 2018; 541(1-2): 1-10.
22. Naeem M, Pervaiz F and Nawaz Z: A quality by design approach: fabrication, characterization and evaluation of optimized transdermal therapeutic system for antirheumatic lornoxicam. Acta Pol Pharm 2017; 74(1): 249-66.
23. Poudel B, Marasini N and Tran T: Formulation, characterization and optimization of valsartan self-microemulsifying drug delivery system using statistical design of experiment. Chem Pharm Bull 2012; 60(11): 1409-18.

How to cite this article:
Kalamkar RV, Wadher SJ and Jain AS: Formulation, characterization and optimization of self- nanoemulsifying drug delivery system for water insoluble drug using statistical design of experiment. Int J Pharm Sci & Res 2020; 11(7): 3507-16. doi: 10.13040/IJPSR.0975-8232.11(7).3507-16.