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Ivermectin Loaded Self Nano Emulsifying Drug Delivery System for the Treatment of Strongyloidiasis: Formulation, Optimization and Characterization

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ABSTRACT: In this study, Ivermectin loaded self-Nano emulsifying drug delivery system (SNEDDS) was developed in order to treat Strongyloidiasis because Ivermectin has poor oral solubility and bio availability. The study was focused on incorporating the drug in lipid based emulsion system for improving oral solubility and thereby enhancing the bio availability. The study involved D-optimal design and the choice of independent variables was oil, surfactant and co surfactant and constraints set for each independent factor. Hydrogenated vegetable oil, tween 80, poly ethylene glycol-400 have the highest solubility of Ivermectin. The optimized SNEDDS of Ivermectin was prepared with the selected lipid, surfactant, co-surfactant showed self-emulsification time 20.54 seconds, globule size of 158.2 nm and percentage transmittance was 99.25. The comparative in vitro drug release studies has proven that the optimized SNEDDS formulation showed rapid drug release rate to that of the marketed formulation.

KEYWORDS: Self-Nano emulsifying drug delivery system, Ivermectin, Optimization, D-Optimal design

I. INTRODUCTION

[1, 2] Crude emulsions are thermodynamically unstable. Class II and III of Lipid formulation classification system (LFCS) represents self Nano emulsifying drug delivery system (SNEDDS) proposed by pouton1. More hydrophilic and lipophilic amphiphiles and precipitation inhibitors provide self-emulsifying properties. Upon dilution or mild agitation, in the GI fluids, these systems transform into oil in water (O/W) emulsions, double emulsions, Micro emulsions or Nano emulsions. Self-emulsification improves the bio-availability of drug substance by the circumvention of drug crystal dissolution, which is often insufficient and highly variable for the poor water soluble drug. Compared to the crude emulsions, SEDDS have better physical and chemical stability. High patient compliance and palatability can be obtained because of its easiness to formulate as capsules or tablets. Compared to other Lipid Based Drug Delivery Systems (LBDDS) food has only minor effect on SEDDS. Other advantages include its quick onset of action, easy of manufacture and scale-up as well.

[3, 4] Water and oil phases tend to separate easily in order to reduce the inter-facial energy. Interface

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between water and oil phases stabilize by formation of a mono layer around the oil droplets which in turn reduces the inter-facial free energy due to the presence of more hydrophilic amphiphiles. In case of SNEDDS, very small amount of energy is needed to form emulsion. Therefore, the processes of emulsification take place rapidly. The readiness of the emulsification is proposed to be related to the ease of water penetration into the various gel or liquid phases formed on the surface of the droplets.

II. MATERIALS AND METHODS

MATERIALS

Ivermectin was obtained as a complimentary sample from Bafna pharmaceuticals, Himachal Pradesh. Olive oil, castor oil, coconut oil, hydrogenated vegetable oil were purchased from local store. Tween 80, Tween 60, Tween 20, PEG-400, Span 60, Span 80 were procured from Kniss Labs, Chennai.

METHODS

SOLUBILITY STUDY:

[5] By using shake flask method solubility of Ivermectin in selected oils, surfactant and co-surfactant was identified. In each vial, 200 mg of drug was added along with each 2 ml of co-surfactant, surfactant and oil. The sealed vials were placed in vortex shaker for 10 minutes and then placed in orbital shaker at 100 rpm for 72 hrs. to attain equilibrium. Then sealed vials were placed in centrifuge for 15 mins at 5000 rpm to separate supernatant and it was diluted suitably with methanol for quantification using UV- visible spectrophotometer at 245nm.

CONSTRUCTION OF TERNARY PHASE DIAGRAMS:

[5] Water titration method was used to identify the best emulsification region for selected surfactant, co- surfactant and oil mixtures. Each one of them was represented by apex of triangle. Surfactant and co-surfactant mixtures concentration ranged from 9:1 to 1:9 were weighed in a screw-cap bottle and vortexed. A pseudo ternary phase diagram was obtained by titrating uniform solutions of surfactant, co-surfactant, and oil. Aliquots of distilled water was added to each mixture in room temperature and visually examined for clarity and transparency. Isotropic and clear solutions were identified as Nano emulsion regions.

OPTIMIZATION USING D- OPTIMAL DESIGN:

[5, 6] D- Optimal design was selected to statistically optimize the independent factors (or) variables to evaluate the main effects, quadratic effects and interaction effects of independent factors (or) variables. Matrix consisting of 3 factors and 3 levels was selected for optimization study. The experimental design consisting of replicated central point of a multidimensional cube with a set of points lying at midpoints of edges.

$$Y = \beta 0 + \beta 1X1 + \beta 2X2 + \beta 3X3 + \beta 12X1X2 + \beta 13X1X3 + \beta 23X2X3 + \beta 11X12 + \beta 22X22 + \beta 33X32$$

Where β0 is the intercept, Y is the dependent variable, β1 to β33 are the regression coefficient and X1, X2 and X3 are the independent variables selected from preliminary experiments.

OPTIMIZATION VALIDATION AND DATA ANALYSIS:

[7] Using design expert software ANOVA was calculated and polynomial equation was statistically analyzed. Prediction error was calculated using comparing experimental values with predicted values. The Independent variables like surfactant, co-surfactant and oil were studied. The responses studied were Globule size, self-emulsification time, and % transmittance.

PREPARATION OF SNEDDS:

[8, 9] Based on the solubility study reports series of SNEDDS formulations were prepared using 6 mg of Ivermectin in selected surfactant, co-surfactant, and oil. The resultant mixture was heated at 40◦C and vortexed until a clear solution was obtained. The SNEDDS formulations were stored in sealed vials at room temperature for further use.

CHEMICAL COMPATIBILITY STUDY:

[8, 9] Chemical compatibility study between selected surfactant, co-surfactants and oil was determined using FT-IR spectroscopy. Surfactant, co-surfactants and oil were mixed with potassium bromide to form pellets and it was observed in FT-IR.

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DETERMINATION OF SELF-EMULSIFICATION TIME:

[9, 10] At 100 rpm in USP type II (paddle) apparatus, 37±0.5 ºC in 0.1 N HCl were used to estimate the emulsification efficiency of self-emulsification time of optimized SNEDDS. 1 ml of optimized formulation was incorporated in 100ml of medium at 100rpm. The self-emulsification time of each formulation was determined.

DETERMINATION OF % TRANSMITTANCE:

[11,12] By using UV-Visible spectrophotometer % transmittance of the prepared SNEDDS was measured by diluting the SNEDDS to 100 folds with distilled water and the absorbance was measured at 650 nm using distilled water as blank,

DETERMINATION OF REFRACTIVE INDEX:

[11, 12] The Refractive index (RI) of prepared SNEDDS was determined using water as standard and the RI value of the water is 1.3330 at 25ºC.

DETERMINATION OF VISCOSITY:

[13] Viscosity of the prepared Nano emulsion formulations before dilution was determined by Brookfield cone and plate rheometer using spindle 25°C ±0.5°C10. The viscosity of SNEDDS after dilution with water was determined. Viscosity of the SNEDDS used to identify the type of emulsion formed. High viscosity indicates o/w type of emulsion and low viscosity indicates w/o type of emulsion.

DRUG CONTENT STUDY OF SNEDDS:

[13, 14] In a 100 ml standard flask, 6 mg of Ivermectin mixed with SNEDDS was transferred, and diluted with 0.1 N HCl to make 100 ml. With a 0.45 filter, the final product was purified. 0.1 N HCl was used to dilute 1 ml of the clear solution to 100 ml. At 245 nm, UV spectrophotometer was used to determine the concentration of the resultant solution.

DISPERSIBILITY TESTS:

[14] Using a typical USP XXII dissolution device, the oral Nano emulsion's ability to self-emulsify was evaluated. Each 500 ml of phosphate buffer (pH 6.8), 0.1 N HCl, and distilled water were added to 1 ml of each formulation at a temperature of 37 ± 0.5º C. The uniformity of the formed Nano emulsion was analysed.

GLOBULE SIZE AND ZETA POTENTIAL ANALYSIS:

[15, 16] The Malvern Zetasizer was employed to determine the average globule sizes (z-average), Zeta potential, and Poly dispersity Index (PDI) of emulsions made from stable SNEDDS formulations. Prior to analysis, each formulation was diluted (100 times) with distilled water to the correct concentration. A 90° angle of observation was used for the analysis at a temperature of 25 °C. The fundamental idea is linked to the Brownian motion of droplet as a function of time, which was governed by variations in light scattering, according to photon correlation spectroscopy.

IN-VITRO DRUG RELEASE STUDY:

[17] In vitro release test was conducted using the Dissolution Apparatus (I.P. type 2) at 37 ± 0.5º C in 900 ml (0.1 N HCl) at 100 rpm. Ivermectin was administered as a single dosage comprising 6 mg in the treated dialysis bag. Periodically, samples were withdrawn, and the same amount of buffer was replaced.

RELEASE KINETICS OF THE OPTIMIZED FORMULATION:

[17] To interpret the drug release kinetics from the formulation, a variety of kinetic models were applied, including the Higuchi model, the Korsemeyer-Peppas model, the First order, and the Zero order. The best- fit model was chosen based on the formulation greatest regression values for correlation coefficients. Data from the dissolution study were analyzed in multiple kinetics models to evaluate the in vitro release kinetics of the optimized formulation.

ACCELERATED STABILITY STUDIES:

[18] The design for stability studies to support the submission of NDAs and MAAs is described in the ICH guidelines Q1A (R2) stability testing of novel drug substances and products.

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III. RESULTS

FTIR STUDY:

Ivermectin, polyethylene glycol 400, hydrogenated vegetable oil, and Tween 80 all had peaks in their FTIR spectra that did not move or lose their distinctive drug-related peaks. This implies that there was no interaction between the excipients and the drug.

SOLUBILITY OF IVERMECTIN:

The SNEDDS formulations were further developed using the ingredients that gave Ivermectin the best solubility. . Non-ionic surfactants have lower micelle concentration values than ionic ones and are less toxic overall. Table no. 1 contains the findings on Ivermectin solubility in various excipients.

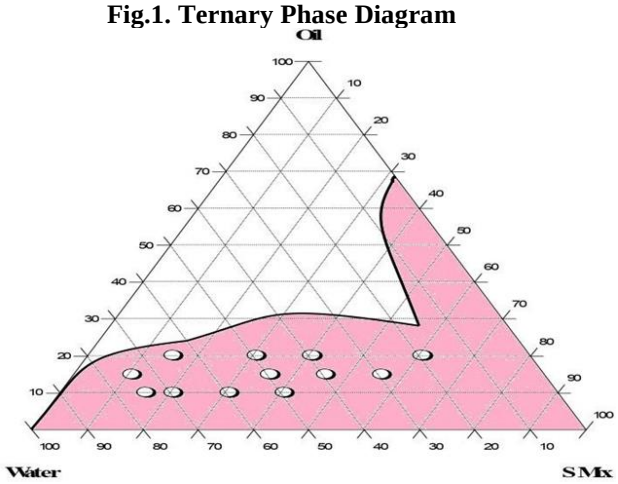
Table No.1. Solubility Study of Ivermectin.

S.NO	SOLVENTS	SOLUBILITY (mcg/ml)
OILS		
1	Castor oil	729.36
2	Coconut oil	849.80
3	Olive oil	740.20
4	Hydrogenated vegetable oil	912.00
SURFACTANT		
5	Tween 80	984.25
6	Tween 60	708.94
7	Tween 20	840.34
CO-SURFACTANT		
8	Span 80	548.12
9	Span 60	678.22
10	PEG-400	828.22

CONSTRUCTION OF TERNARY PHASE DIAGRAM:

The region of the w/o type nano emulsion discovered by the water titration method was located in the region of the ternary phase diagram using the ternary plot generator. Water was used to titrate different oil-surfactant mixture ratios, and the resulting nano emulsion region is shown in Fig. 1.

Fig.1. Ternary Phase Diagram



D- OPTIMAL DESIGN:

Transmittance (Y3), globule size (Y2), and Self-emulsification time (Y1) were used to evaluate the quality of the SNEDDS formulation. The formulation contained 20%-50% surfactant, 20%-50%, and co surfactant (Y3) to estimate the experimental error and the design's precision. Using Design-Expert software, at three factors total of 16 trial runs were created and assessed. In Table No.2, a summary of the experiment's design was provided.

Table No. 2. Summary of Experimental design

Independent variables	Units	level		
		-1	0	+1

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X1= Oil	% W/V	10	15	20
X2= Surfactant	% W/V	20	35	50
X3= Co-surfactant	% W/V	20	35	50
Dependent variables	Units	Constraints		
Self-emulsification time	Seconds	Minimize		
Globule size	Nanometer	Minimize		
% Transmittance	%	Maximize		

EFFECT OF FORMULATION VARIABLES ON CHARACTERISTICS OF SNEDDS:

Effect of the formulation variables, co- surfactant concentration (X3), surfactant concentration (X2) and lipid concentration (X1) on % Transparency (Y3), and Globule size (Y2) and self-emulsification time (Y1) was studied by utilizing D-optimal design. The levels of formulation variables and processing variable were selected on the basis of preliminary studies. The findings were presented in table No .3. The results of response were fitted into polynomial models and ANOVA for the determination of the model statistical significance. It was observed that the responses Y1, Y2, Y3 were best fitted into the quadratic response surface model (P value for Y1, Y2, Y3 is less than 0.0001) which shows that the model is significant. From Design Expert® software the polynomial equations in terms of coded factors are given below.

Sid	Run	Factor 1 Oil	Factor 2 Surfactant	Factor 3 Co-surfactant	Response 1 Self emulsification time	Response 2 Globule size	Response 3 % Transmittance
1	1	19.89211	44.94211	35.16578	42.09	185.65	97.89
2	2	14.12332	50	35.87668	25.36	170.45	98.25
3	3	14.35518	45.51713	40.12769	27.89	173.45	98.9
4	4	10	44.9	45.1	20.15	161.78	99.25
5	5	14.17891	35.82109	50	26.35	170.87	98.54
6	6	20	50	30	52.48	189.45	96.96
7	7	18.49734	40.65644	40.84622	34.58	180.98	97.79
8	8	20	50	30	49.75	189.26	96.53
9	9	20	30	50	50.19	191.45	96.25
10	10	10	40.16848	49.83152	20.54	158.2	99.25
11	11	18.49734	40.65644	40.84622	31.25	178.65	97.89
12	12	14.36041	40.13959	45.5	25.19	167.58	98.78
13	13	20	30	50	61.23	191.12	96.56
14	14	14.17891	35.82109	50	26.69	169.87	98.56
15	15	14.12332	50	35.87668	27.45	159.32	98.67
16	16	20	35.00462	44.99538	54.76	192.58	97.23

Table No.3. Actual summary of D-Optimal design for Ivermectin SNEDDS

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Y1 S-M time =+25.06680* oil+3.14679 * Surfactant+2.74215 * co Surfactant-0.53812 * oil * Surfactant-0.63121 * oil * co Surfactant-0.019321 * Surfactant * co Surfactant.

Y2 Globule size =+5.42469* oil+0.71681 * Surfactant+0.84071 * co Surfactant.

Y3 % transmittance =-1.20952 * oil+1.71086 * surfactant +1.78296 * co surfactant +1.022228 * oil * Surfactant +1.415934 * oil * co Surfactant +8.46059E-004 * Surfactant* co Surfactant.

The polynomial equations provide the quantitative effects of the formulation variables X3, X2, and X1 and their interaction effects on the answers Y3, Y2, and Y1. If a model follows the present model of the study and the P value is at a 95% confidence interval (0.05), the model will be deemed significant.

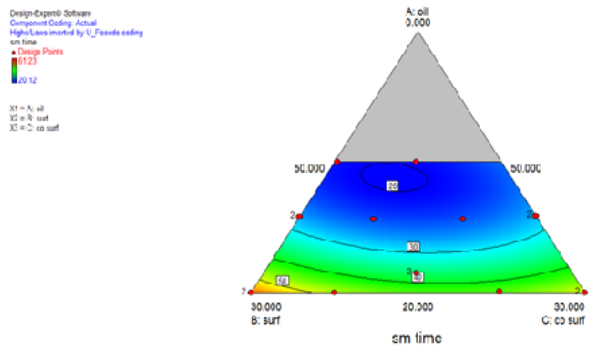

Fig 2a. Contour Plot for Response 1(Self emulsification Time)

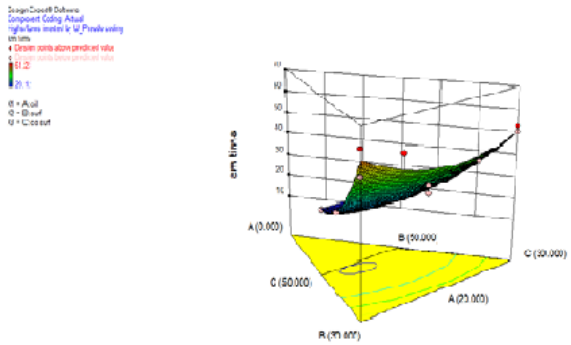

Fig 2b. 3D Plot for Response 1 (Self emulsification time)

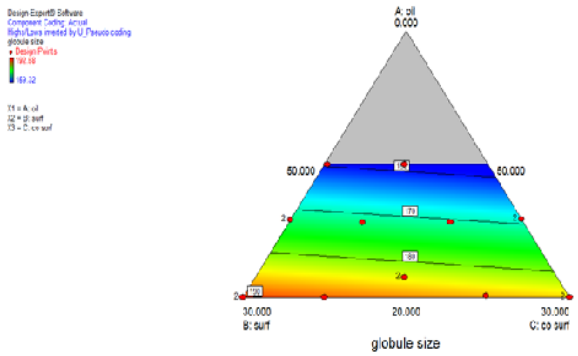

Fig 3a. Contour Plot of Response 2 (Globule Size)

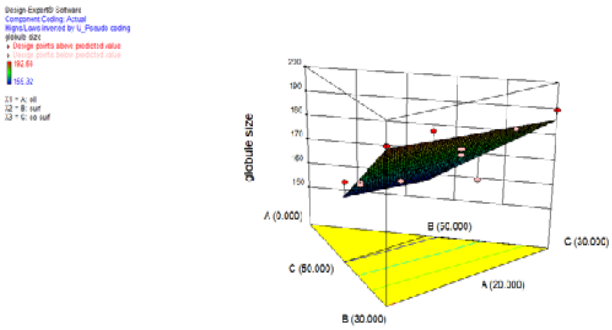

Fig 3b. 3D Plot for Response 2 (Globule Size)

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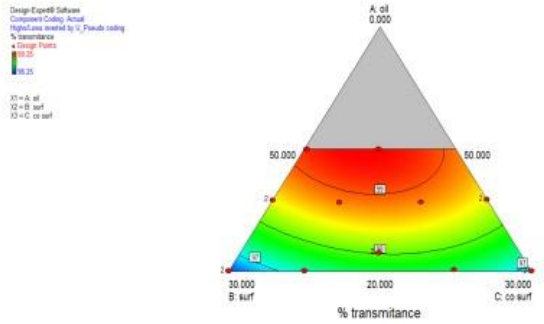

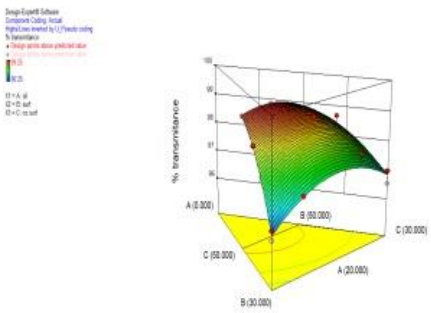

Fig 4a. Contour plot for Response 3 (% Transmittance) **Fig 4b. 3D plot for Response 3 (% Transmittance)**

Parameters	Predicted Value	Actual Value	SE Mean
Self-Emulsification Time (Sec)	22.87149	20.54	1.95075
Globule Size (nm)	160.1308	158.2	1.06090
% Transmittance	98.62124	99.25	0.35245

OPTIMIZATION:

The optimal conditions were calculated by using numerical optimization approach along with the desirability study in Design Expert software. The optimal parameters obtained were to use 10 % w/v of lipid, 41.16% w/v of surfactant and 49.83% w/v of co surfactant. The self-emulsification time, globule size and %Transparency of the optimized Ivermectin loaded SNEDDS was found to be 20.54 seconds, 158.29 nm and 99.25%. The findings were listed in table number 4, 5.

Response factor	Model				Lack of fit	
	F-value	Prob >F	R2	Adequate precision	F-value	Prob >F
Y1	29.05	<0.0092	0.9366	14.25097	1.42	0.050
Y2	45.09	< 0.0021	0.8740	16.91413	1.74	0.063
Y3	54.65	<0.0061	0.9646	20.76396	1.16	0.050

TABLE NO. 4. MODEL SUMMARY STATISTICS

TABLE NO. 5. COMPARISON OF PREDICTED AND ACTUAL VALUES OF OPTIMIZED FORMULATION

DETERMINATION OF REFRACTIVE INDEX (RI):

The refractive index (RI) of formulation was found to be 1.3390. At 25° C, water's RI is 1.333250. All formulation RI values were close to those of distilled water shows that it's close to region of Nano emulsion.

DETERMINATION OF pH AND DRUG CONTENT:

The pH of the SNEDDS was found to be 6.68 ± 0.03. SNEDDS formulations were determined to contain 99.54 percent of drugs.

PRECIPITATION AND PHASE SEPARATION STUDY:

By diluting SNEDDS formulations in 0.1 N HCl for 100 times, phase separation investigations show the formulations are stable for 48 hours. No phase separation or drug precipitation occurs.

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DISPERSIBILITY TEST:

A dispersibility test was used to quantify the SNEDDS formulation stability. The SNEDDS formulation were added to a variety of media, including water (neutral), strongly acidic (0.1 N HCl) and Weak acidic media (Phosphate buffer pH 6.8). The ideal formulation exhibits quick dispersion without precipitation and separation in all three media.

DETERMINATION OF VISCOSITY:

SNEDDS diluted and undiluted viscosity was measured. The viscosity of SNEDDS before dilution in centipoises was observed to be 84.2, and the viscosity after dilution with water is 0.8872.

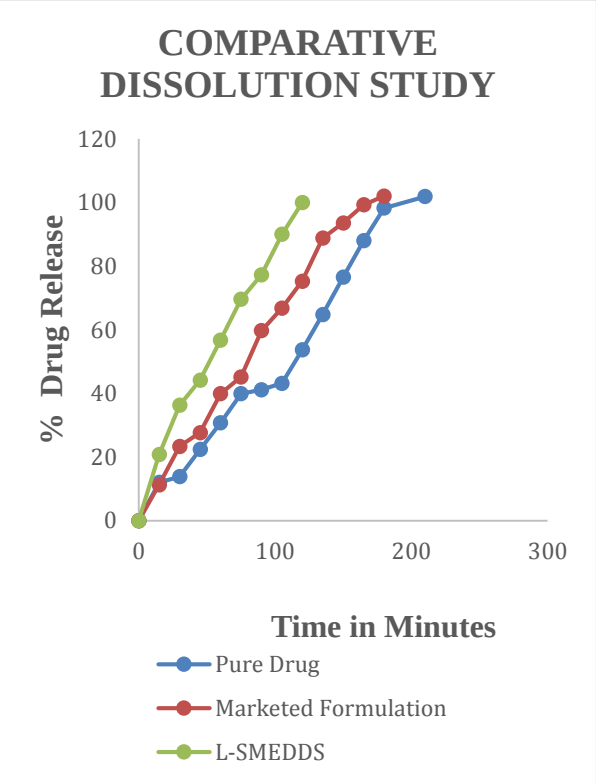
ZETA POTENTIAL ANALYSIS:

Zeta potential could be used to quantify the strength of the attraction or repulsion between globules. The optimized SNEDDS have a zeta potential and poly dispersibility index of -0.3 mV and 0.087, respectively.

IN VITRO DRUG RELEASE OF OPTIMIZED FORMULATION:

In comparison to (pure drug), the developed optimized Ivermectin loaded SNEDDS formulation exhibited a much greater rate of solubility. It was found that adding the drug to the lipid-based drug delivery system boosted the drug's rate of release. Compared to commercial formulations, the Ivermectin loaded SNEDDS formulation displayed a quick first burst during in vitro release. The optimized formulation's in vitro release was shown in Fig 5.

Fig. 5: *In vitro* % Drug release of optimized formulation



RELEASE KINETICS OF THE OPTIMIZED FORMULATION:

When compared to the R2 value of the first order equation, the R2 value of zero order equation had an R2 value that was nearly 1. The Higuchi equation's slope was greater than 1, indicating that Higuchi kinetics of release are used to explain it. The Korsemeyer-Peppas equation's 'n' value, an exponent, was 0.718, showing that non-Fickian diffusion governs the mass transfer. The release via erosion process is indicated by the large disparities between the R2 values of the Hixson-Crowell equation and the Zero order equation.

ACCELERATED STABILITY STUDY:

In order to evaluate the stability of the optimized SNEDDS, the formulation was put into airtight glass vials, and the vial was subsequently subjected to stability experiments at 40˚C± 2 ˚ C/ 75% ±5% RH for a period of three months. Samples were placed in stability chambers with temperature and humidity controls. We evaluated the samples'

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transparency, phase separation, precipitation, medication concentration, and pH. The results of the accelerated stability studies are presented in Table 6.

Table no. 6. Accelerated stability studies.

Testing period	Changing of Physical appearance		pH	Drug content (%w/w)	Phase separation and precipataion
	Color	Odor			
Day 0	NC*	NC*	6.84	101.53	NO
Day 15	NC*	NC*	6.86	101.53	NO
Day 30	NC*	NC*	6.84	100.50	NO
Day 60	NC*	NC*	6.88	99.90	NO
Day 90	NC*	NC*	6.90	98.50	NO
Day 180	NC*	NC*	6.90	98.54	NO

*- No Change

IV. DISCUSSION

By adopting a D-optimal design, the primary objective of this study was to determine how formulation variables including co-surfactant concentration (X3), surfactant concentration (X2) and lipid content (X1), affected percentage transparency (Y3) globule size (Y2) and self-emulsification duration (Y1).The optimized Ivermectin loaded SNEDDS formulation was characterized for its refractive index, pH, viscosity, dispersibity, phase separation, thermodynamic stability, Zeta potential, and poly dispersibity index. It was observed that decreased lipid concentration produces lesser globule size and increase in % transparency perhaps of more interest, concentration of surfactant and co surfactant affected both response variables globule size and self-emulsification time. The optimal conditions obtained were: 10 % w/v of lipid, 41.16% w/v of surfactant and 49.83% w/v of co surfactant. The self-emulsification time, globule size and %Transparency of the optimized Ivermectin loaded SNEDDS was found to be 20.12 seconds, 155.29 nm and 99.1% respectively.

V. CONCLUSION

The goal of this study was to create SNEDDS that were loaded with Ivermectin to increase solubility and minimize dosing frequency to promote patient compliance. The findings imply that the SNEDDS technique could be a potential substitute for the traditional oral formulation for poorly soluble medications like Ivermectin in order to increase its bioavailability.

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