

Mirtazapine Loaded Solid and Liquid Self-Emulsifying Delivery System and Characterization with Neural Network Start (NNS) Modelling

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ABSTRACT: Background: Mirtazapine (MTZ) is delivered via a self-emulsifying system (SEDDS) to treat depression by acting as an antagonist at multiple serotonin and adrenergic receptors. **Aim:** The goal of SEDDS formulation preparation is a 2-level factorial design using a selected combination of three components such as X1- surfactant and co-solvent (Smix) (Tween80&PEG400) at upper level 1:5 and lower level 1:1 ratio, X2- stirrer speed (rpm), X3- stirring time (min), and to evaluate the produced SEDDS. **Materials and methods:** The two-level factorial design with a Design Expert used in formulation assessed physicochemical features such as pseudo-ternary phase design, emulsification, phase separation, pH, percent transmittance, permeability studies, ex vivo drug release, liquid (LSEDDS) to solid SEDDS conversion, flow properties, entrapment efficiency, cloud point, drug excipient compatibility studies, stability studies, and optimization. **Results:** The Neural Network Start (NNS) was used in the optimization, feed-forward back propagation Levenberg-Marquardt Algorithm, and performance was measured using the mean square error (MSE). NNS with ten units of layer size provided a better fit for all responses ($R^2 = 0.99996, 0.999, \text{ and } 0.98$ for T100, T50, and PD 20) than multiple linear regression (MLR) (0.9517, 0.9998, and 0.7942 for T100 (time required for 100% drug release), T50 (time required for 50% drug release), and PD 20 (percentage drug release 20 minutes), respectively). **Conclusion:** The dissolution of drug release in LSEDDS and SSEDSS is substantially better than in pure MTZ. LSEDDS and SSEDSS formulations demonstrated appropriate stability for 90 days according to ICH stability quality requirements, including emulsification time, phase separation, angle of repose, and drug content. The SEDDS were successfully designed to increase the oral bioavailability of MTZ, allowing for larger therapeutic applications.

Keywords: Mirtazapine, Surface adsorption, Stability, Flow properties, in vitro.

INTRODUCTION

Mirtazapine (MTZ), a BCS Class II medication, increases the release of norepinephrine and serotonin in the brain, as seen in Figure 1. It has also been shown to be an antagonist at various serotonin and adrenergic receptors [1, 4]. The recent literature review on various designs of MRT was significantly boosted in formulated aquasomes[5], co-processed excipients have considerable promise in increasing release[6], increased solubility of MTZ with improved percentage relative bioavailability to 153% [7], embedded in-gel demonstrated successful transdermal drug permeation[8], and floating sustained are reported[9]. SEDDS technology increased the solubility and the bioavailability of many weakly water-soluble medications. However, SEDDS as liquid formulations has various limitations, including low drug loading capacity, drug leakage, low stability, and a limited range of dose forms. To circumvent these restrictions, liquid SEDDS (L-SEDDS) can be changed to solid dosage forms using diverse procedures such as filling capsules with liquid or semi-solid SEDDS and adsorbing them to a solid carrier. A current literature study on various SEDDS is used to

solve low bioavailability issues in poorly soluble and highly permeable compounds, according to in silico formulations, increase cannabidiol bioavailability, atorvastatin adsorbed on solid carriers, hydrophobic drugs, ciprofloxacin, silymarin, cromolyn sodium, benznidazole, and hydrophobic drugs, allowing them to enter formulations by oral administration[10, 18]. The SEDDS formulation is administered in the GIT, where it comes into contact with GI fluid and forms a self-emulsion, resulting in drug solubilization. The current study's objective was to perform SEDDS formulation of MTZ and design statistically using a 2-level factorial design with a selected combination of three factors such as X1- concentration of surfactant and co-solvent (Smix) (Tween80&PEG400) at higher levels 1:5 and lower levels 1:1 ratio, X2- Stirrer speed (rpm) at higher levels 200rpm and lower levels 150rpm, and X3- Stirring Time (min) at higher levels (+) of 25 min. Furthermore, lower levels (-) of 15 min. (+) represent a higher level, (-) indicates a lower level, and Central (0) is shown in (Table 1). The individual and combination elements that significantly increase formulation performance are described [19, 24].

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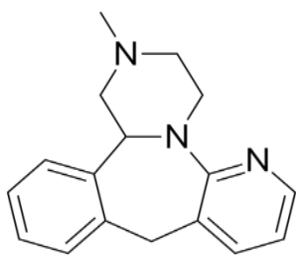


Figure (1): Structure of MTZ.

METHODS

Materials

Mirtazapine, A complimentary from Newland Pvt. Ltd. in Hyderabad, Tween 80 & PEG 400 was acquired from Merck Specialties Pvt. Ltd., Mumbai, and castor oil from Swastika Jaya Products, Bhimavaram.

Pseudo-Ternary Phase Design

The varied proportions of surfactants co-surfactant (Smix) (1:1, 1:2, 1:3, 1:4, and 1:5w/w) [45]. In brief, Smix and oil were mixed at varied volumes such as 1:9, 2:8, 3:7, 4:6, 5:5, 6:4, 7:3, 8:2, and 9:1 in the pre-weighed conical flask, oil- surfactant- co-surfactant with water under moderate stirring, equilibrated, observed visually and determined as being microemulsions and design by Ternaryplot.com[25].

Design of Experiments (DOE.)

The SEDDS formulation has 3 factors and 2-levels factorial designs to find the individual combined response of additives on drug release. The concentrations of Smix (X1), Stirrer speed (X2), Stirring time (min) (X3). The effect of 3 factors on dependent variables (Y1: T100 (time required 100% drug release), (Y2: T50 (time required 50% drug release), and (Y3: PD20 (% drug release 20 min.) were studied using DOE, which was reported previously. The experiments are shown in (Table 1)[19, 24].

Formulation of Liquid SEDDS (LSEDDS)

The required amounts of castor oil, tween80, and PEG400 were used. The PEG was in a beaker, slightly heated by a magnetic stirrer; castor oil was blended with tween 80, mixed thoroughly, and drug added (specified time & rpm). The total mixture was properly homogeneous [30, 33, 44].

Emulsification

A USP Type II was employed to investigate emulsification. 1 milliliter was added to 900 milliliters of distilled water at 37±0.50C and 100 rpm for agitation [34]. The visual performance of formulations was assessed, as shown in (Table 2).

Phase Separation Study

Formulations were diluted 100 times with distilled water. The tested formulations were maintained at 25°C for 24 hours and visually evaluated for phase separation.

pH

The pH was measured by accurately weighing 0.5 milliliter of a sample and 10 milliliters of water to dissolve the sample; the pH was determined at room temperature using a digital pHmeter. The performance friendliness and biological compatibility of this application are confirmed.

UV Analysis

To obtain 10-70µg/ml (microgram/milliliter), 10 milliliters (1 milliliter/ml) were transferred to a 100-milliliter volumetric flask and diluted with 0.1N hydrochloric acid buffer. The absorbance

of these solutions was measured at 232nm with a UV (ELICO Double Beam SL 210) (n = 6).

Determination of Transmittance (%)

It was diluted 100 times with water, and the % transmittance at 232 nm was measured with a UV spectrophotometer.

Ex-vivo drug release

A portion of female sheep skin was cut and inserted in the area between the donor and receptor compartments of the diffusion cell introducing M4 formulation, with the dorsal side up, 0.1 N Hydrochloric acid buffers were used as a dissolution media, with the temperature fixed at 32°C and the sample retrieved at appropriate time intervals (n=4). A UV at 232nm was used to analyze the sample.

Permeability studies

The chick's duodenum was isolated, and the tissue was extensively cleaned with Ringer's solution[46]. A syringe was used to inject the sample into the duodenum, and the two ends of the intestine were firmly connected before being placed in an organ bath with constant aeration and filled with 0.1N hydrochloric acid buffer, absorbance estimate by UV at 232 nm.

Conversion of LSSDDS to Solid SEDDS (SSEDSS)

The SSEDSS was prepared by the Surface adsorption method by using solid carriers such as magnesium stearate, lactose, and talc for solidification. The solidification is performed using the surface adsorption method. An accurate quantity of lactose, approximately 5-5.5 gm, was mixed with LSEDDS volume 1 milliliter, with lactose acting as adsorbing agent in a vessel. The final formulation was uniformly homogenized; the mass was passed through sieve 12 and dried in the oven (Temp. 60-700c).

Flow properties

The Flow properties were assessed by using an angle of repose (AR), Carr's index (CI), Bulk density (BD), true density (TD), and Hausner's ratio (HR), which were reported earlier [36-37].

Entrapment Efficiency (EE.)

The formulation with 250 milliliters of water stirred for 10 minutes, and 2 milliliters of the sample was removed, centrifuged, and estimated using a UV. The EE was determined by

$$= \frac{\text{drug in formulation}}{\text{Drug added}} \times 100$$

Cloud Point

The formulations were diluted one-to-100 with distilled water, placed in a water bath at 37 °C, and the temperature was gradually increased until cloudiness appeared [37].

Effect of Robustness

The LSEDDS were diluted in 0.1N hydrochloric acid 50, 100, 500, and 1000 times, and the mixtures were held for one day to observe phase separation. The LSEDDS was used to simulate the physiological dilution process following oral delivery.

FTIR

The FTIR samples were collected using the Kbr disc method on a Bruker ALPHA -, with a resolution of 1 cm⁻¹ and a scanning range of 4000-600 cm⁻¹.

In Vitro dissolution

The USP type II (LAB INDIA DS-8000) was utilized, and the SSEDSS were placed in hard gelatine capsules (size 00) and dissolved. As a dissolution media, 900 milliliter of 0.1N hydrochloric acid was kept at 37±2 °C and agitated at 50 rpm. The samples (5 milliliters) were taken at 10, 20, 30, 40, 50, and

60-minute intervals and replaced with an equivalent volume of 0.1N hydrochloric acid buffer and MTZ. Concentrations were measured by UV spectroscopy.

In Vitro/ Ex Vivo Correlation

Calculate between in vitro and ex vivo drug release profiles with M2 formulation release 100% within 40 min.

Globule size and Zeta potential determination Optimized formulae

In a glass beaker with constant stirring, 5 milliliters of each LSEDDS formulation was diluted with 250 milliliters of distilled water, and the globules formed and polydispersity index was assessed using a Zetasizer (Nano ZS).

Stability studies

The samples were stored for 90 days under accelerated circumstances (40 ± 2 °C, $75 \pm 5\%$ RH), and stability tests were performed on the emulsification, phase separation, angle of repose, and drug contents up to 90 days at the time of manufacturing and after processing [38].

Neural network start (NNS) modeling

Train a neural network with the backpropagation method Levenberg-Marquardt Algorithm used for the MATLAB Neural Network Toolbox learning process. The (X1) surfactant and co-solvent (Smix) (Tween80&PEG400), X2- Stirrer speed (rpm), X3- Stirring Time, three inputs, 3 output units T100 (Y1), T50 (Y2) and PD 20(Y3) were used in the developed networks. The optimum network model was explored with several trials, and training was considered to Mean square error; R^2 values were reached, and the appropriate network structure was determined [50, 52].

Statistical Analysis

The release kinetics were evaluated by using first & zero-order kinetic models reported [39, 43]. The Dissolution parameters were subjected to analysis of variance (ANOVA) by using DOE.

RESULTS

SEDDS, when introduced into aqueous media from an o/w emulsion, because of good agitation of the surfactant and co-solvent absorbed at the interface, reducing interfacial tension. The ternary phase diagrams were created in order to locate the self-emulsifying zone.

Emulsification studies (ES.)

The formulation M3 (35sec), M4 (25sec), and M7 (23sec) rapidly formed an emulsion with a clear appearance assessed as grade-A. The formulations M1 (50 sec), M2 (55 sec), and M5 (56sec) rapidly form a slightly less clear emulsion with a white appearance exhibiting grade -B. The M6 (1.12min) and M8 (1.40 min) form a fine milky emulsion that exhibits grade -C.

pH

The pH of all prepared LSEDDS was 5.0 – 6.3, as shown in (Table 4).

Cloud Point Measurement (CP.)

Non-ionic surfactants, Smix ratios, and drug hydrophobicity influence the CP in SEDDS formulations. The CP reach, a further increase in temperature can cause phase separation (PS) in formulations containing non-ionic surfactants, dehydration of polyethylene oxide, and can affect the drug absorption. The CP of formulations 61.2 to 69.110C is shown in (Table13).

UV Analysis

Figure3 depicts the standard curve of 10 to 70 µg/milliliter, yielding the equation $y = 0.0128x + 0.005$ and an R^2 value of 0.9985 (Figure3).

%Transmittance

If the transmittance M1 to M_{cp} is greater than 90%, formulations have a transparent; the findings of a percentage transmittance value more than 90% indicate their clarity; this could be owing to the smaller globule size, which increases the emulsion's transparency, the high capacity with led to increased bioavailability.

EX –VIVO drug release

The Ex –vivo drug release LSEDDS were studied (M4) 100% of drug release within 40 min (Figure7).

Flow properties

1. AR: The AR for all the formulations was 14.3 – 30.0, showing excellent flow properties.
2. b) BD.: The BD of all the formulations was found to be 0.45 – 0.55 (gm/cc). c) TD.: The TD of all the formulations was found to be in the range of 0.59 – 0.95 (gm/cc) d) CI: The CI of all the formulations was found to be in the range of 10.16 – 26.2% are shown in good to fair to passable, e) HR: The HR of all the formulations was found to be in the range of 1.11 – 1.43 respectively are shown in good to fair to passable.

EE.

The EE of all formulations of SSEDSS was greater than 80%, so the drug content fulfillslabeled claims shown in (Table13).

In Vitro Dissolution

The drug release from different formulation M1 100% drug release until 30mins, M2 100% drug release until 40mins, M3 100% drug release until 60mins, M4 100% drug release until 40mins, M5 100% drug release until 50mins, M6 100% drug release until 60mins, M7 100% drug release until 60mins, M8 100% drug release until 30mins, M_{cp} 100% drug release until 50mins. The results collected from in-vitro drug release investigations are applied to the mechanism of drug release from SSEDSS, such as the zero-order, first-order kinetic model (Table 6). The formulations' correlation coefficient was larger when fitted to the first-order equation, indicating that the first-order release occurs in all formulations.

Design of Experiments

The impact of important factors on the T100 (Time for 100% release), T50 (Time for 50% release), and PD 20 (% release 20 min) SSEDSS was investigated using the 2-level factorial design. The responses T100, T50, and PD20 were found to be in the ranges of 30.0 to 60.0 min, 6.0 to 25.5, and 20.8 to 97.9% due to factors of variables. The contour plots and 3D surface plots are shown in (Figure8), (Figure 9)&(Figure10). The adequacy of the replies was validated by the ANOVA and statistical parameters ($p < 0.05$) significant displayed in (Table 8), (Table9), Table (10) and (Table12), which also highlights the major variables on the development of the SEDDS responses T100, T50, and PD20. The mathematical equations for the replies were calculated in terms of coded factors and are given in Equations (1)-(11). The positive sign indicates a synergistic; a negative sign indicates an opposed effect.

$$(Y1) \text{ Sqrt}(T100) = +6.86676 - 0.27099 X1 + 0.0843624 X2 + 0.27099 X3 - 0.651548 X1X2 - 0.12747 X1X3 - 0.482823 X2X3 - 0.0843624 X1X2X2 \text{-----} 1$$

$$(Y2) \text{ Sqrt}(T50) = +3.36289 - 0.128854 X1 - 0.136355 X2 + 0.522277 X3 + 0.31943 X1X2 + 0.255961 X1X3 - 0.27956 X2X3 + 0.564786 X1X2X3 \text{-----II}$$

$$(Y3) \text{ Log}_{10}(\text{PD}20) = +1.93384 + 0.00991135 X1 + 0.0097821 X2 - 0.00181686 X3 + 0.0244812 X1X2 - 0.00603594 X1X3 + 0.0227592 X2X3 - 0.0151283 X1X2X3 \text{-----III}$$

Above coded equation shown, Equation –I, In the instance of Y1, X1 demonstrated an opposite effect and X2, X3 demonstrated an enhanced effect; Equation –II- in the case of Y2, X1, and X2 demonstrated the opposite, and X3 demonstrated an enhance; and equation –III- in the case of Y3, X1, X2, and X3 demonstrated opposites. The Y1 stirrer speed (rpm) and stirring time play an important role; however, Y2 stirring time plays a significant role, and Y3, Smix(Tween80:PEG400) concentrations and stirrer speed plays an important role, in the case of Y1, as the concentration of Smix(Tween80:PEG400) reduced, stirrer speed and stirring time increased. In the case of T50, as the concentration of Smix(Tween80:PEG400) was reduced, the stirrer speed was reduced, and the stirring time increased [49]. In the case of PD 20, as the concentration of Smix(Tween80:PEG400) increases, the stirrer speed increases, and the stirring time decreases. The summary (Table 11) Correlation coefficient (R^2), Coefficient variance (CV %), Standard deviation, and Adeq. Precision relative to its obtained from the best fitting MLR models.

Permeability studies

The total percentage release was substantially higher for the SEDDS; within one hour, 90.5% of the medication was dispersed from the LSEDDS.

Drug excipient compatibilities

The FTIR spectrum of Mirtazapine is shown in (Figure 4), with characteristic peaks observed at 3615 cm^{-1} (N-H stretch), 3218 cm^{-1} , 2935 cm^{-1} (C-H stretch), 2362 cm^{-1} (C-C stretch), 1572 cm^{-1} (N-H bending), 1427 cm^{-1} (C-H bend plane), 1270 cm^{-1} , 951 cm^{-1} (C-O stretch), 822 cm^{-1} , 756 cm^{-1} (Due to N-H rocking), 699 cm^{-1} , 655 cm^{-1} (Due to C-H rocking), confirming the drug structure.

In Vitro/ Ex Vivo Correlation

Ex Vivo (M2) and M2 SSEDSS were $R^2 = 0.9250$ and $R^2 = 0.9316$, respectively. The model showed higher data fitting for the curved form (Figure 7).

Globule size and zeta potential

SEDDS were distinguished by droplet sizes less than 400 nm, and globule size and polydispersibility index (PDI) were determined to be 329.1 nm and 0.283, respectively. After dilution with water, a PDI of less than 0.3 indicates good consistency in the globule size distribution.

Stability

Furthermore, the self-emulsification was proven to have maintained its initial state when the LSEDDS formulation was dispersed in distilled water for 90 days; the angle of repose exhibited excellent flow, and drug content was $97 \pm 5\%$, but the dispersion remained stable (Table 7).

DISCUSSION

The phase diagram increase in the self-emulsifying zone is shown in (Figure 2). The diagrams were concentration of castor oil, Tween 80 & PEG 400 to identify pseudo ternary phase diagram was marked in blue color, best self-emulsifying of 1:5 castor oil, tween 80 & PEG 400 were selected for future studies. The surfactant reduces the interfacial tension between the oil and aqueous phase and facilitates the dispersion and

formulation of the o/w system; ESis shown in (Table 3). The CP of all formulations was greater than 37 °C, indicating that they will be stable in vivo. The results of a percentage transmittance value greater than 90% suggest their clarity; this might be due to the smaller globule size, raising the transparency of the emulsion. The Ex-vivo drug release LSEDDS were studied (M4) 100% of drug release within 50 min shown in (Figure 7). The flow properties are shown in (Table 5). The release of MTZ from optimized SSEDSS is illustrated in (Figure 5) & (Figure 6) drug release was greatly increased in formulation SEDDS compared to pure drugs. The other kinetic parameters, such as T100, T50, and PD20 were shown in (Table 6). The desirability value was 0.8634, as shown in Figure 10, and independent variables such as X1, X2, and X3 were found in 1:3 ratios Smix, 175 rpm, and 20 min, and Y1, Y2, and Y3 were 31.48 min, 8.04 min, and 93.9828%, respectively, SEDDSs were formulation achieved biopharmaceutical consideration was reported [42, 45]. The optimized product is shown in (Figure 11). The zeta potentials may be regarded as stable if their negative zeta potential was more than -25 mV; SSEDSS had a zeta potential of -26.1 mV, indicating a stable formulation of produced SSEDSS.

Confirmation of the Results

The results were confirmed with a 95% confidence level, as shown in Table 10, which displays the results. Using a factorial design, the researchers created MTZ-loaded SEDDS with low values of all formulation factors T100, T50, and PD20.

Artificial Neural Network applications

Levenberg-Marquardt Algorithm Learning method neural network fitting results are given in (Figure 12).

Comparison of NNS and MLR Models

To compare examined models, results indicated a better predictive ability than the MLR model with R^2 of 0.99996, 0.999, and 0.98 for T100, T50, and PD 20, respectively, compared to the multiple linear regression MLR models 0.9517, 0.9998, 0.7942 for T100, T50 and PD 20 respectively.

CONCLUSION

The LSEDDS with castor oil as the oil phase, tween80 as the surfactant, and PEG400 as co-surfactant were developed; an attempt has been made to develop lactose as an effective carrier for SSEDSS, lactose to be an effective carrier for SSEDSS exhibit excellent EE & micrometric properties. Based on emulsification, drug release from Ex-vivo and in vitro studies was finally successfully performed using factorial design. The SEDDS system has promising potential in enhancing the oral bioavailability of BCS Class II drugs. The NNS modeling with good prediction capability has been developed.

Ethics approval and consent to participate

Not applicable

Consent for publication

The authors give the Publisher the Author's Permission to publish the work

Availability of data and materials

All data generated for this study is included in the article

Author's contribution

Taraka Ramarao Challa.; conceptualization, writing-original draft, data curation, formal analysis, investigation, methodology, project administration, resources, visualization, and writing review & editing, Krishnaveni Akula.; writing review & editing, Kiranmai; methodology, Manisha; visualization, Jayasri; formal analysis, Narendra; project administration, resources, Manikantha; visualization, Tulasi; visualization, Raghunadha; Gupta software, supervision and validation

Competing interests

The authors have no conflicts of interest

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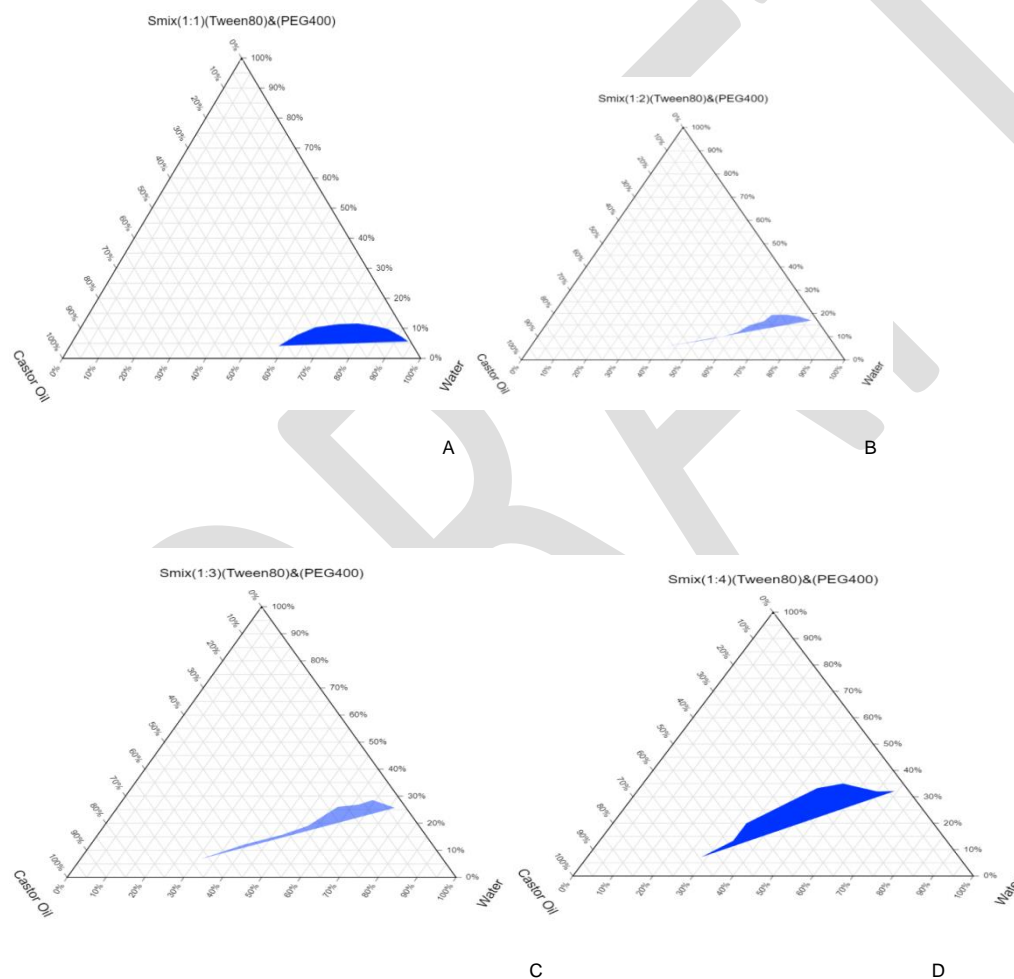
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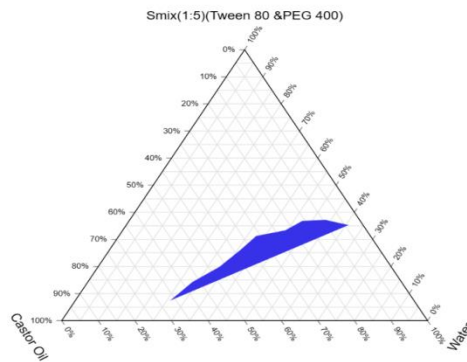
Table (1): Coded formulation for Mirtazapine as per Factorial design.

Independent Variable	High Level(+)	Medium Level(0)	Low Level(-)
(X1)Smix(Tween80:PEG400) ratio	1:5	1:3	1:1
(X2) Stirrer Speed(Rpm)	200	175	150
(X3)Stirring Time(Min)	25	20	15

Table (2): Emulsification Grading.

Grade	Characteristic	Time(min)
A	Rapid Clear Appearance	1
B	slightly less clear emulsion	1
C	milky emulsion	2
D	slightly oily appearance	>2
E	poor emulsification on the Surface	>2





E

Figure (2): Construction of Ternary Phase diagram with Castor oil, Smix and water system A. 1:1(Oil: Smix), B. 1:2(Oil: Smix) C. 1:3(Oil: Smix) D. 1:4 (Oil: Smix) E. 1:5(Oil: Smix) ratio's.

Table (3): Emulsification study of different LSEDDS

Formulation	Grade	Emulsification time(Min. Sec)
M1	B	0.50
M2	B	0.55
M3	A	0.35
M4	A	0.25
M5	B	0.56
M6	C	1.12
M7	A	0.23
M8	C	1.40
MCP	B	0.53

Table (4): pH of various LSEDDS formulations.

FORMULATION	pH
M1	5.0
M2	6.1
M3	5.4
M4	6.2
M5	6.3
M6	5.4
M7	5.3
M8	5.5
MCP	6.2

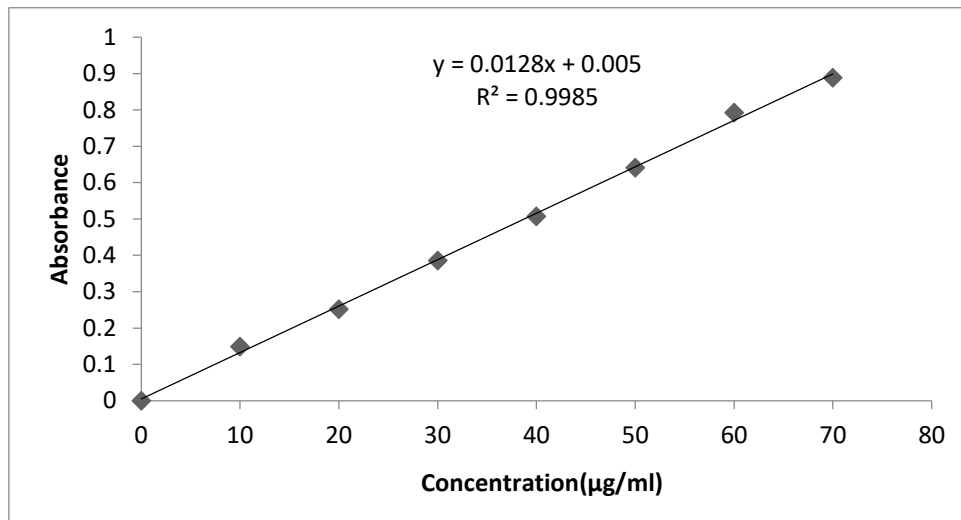
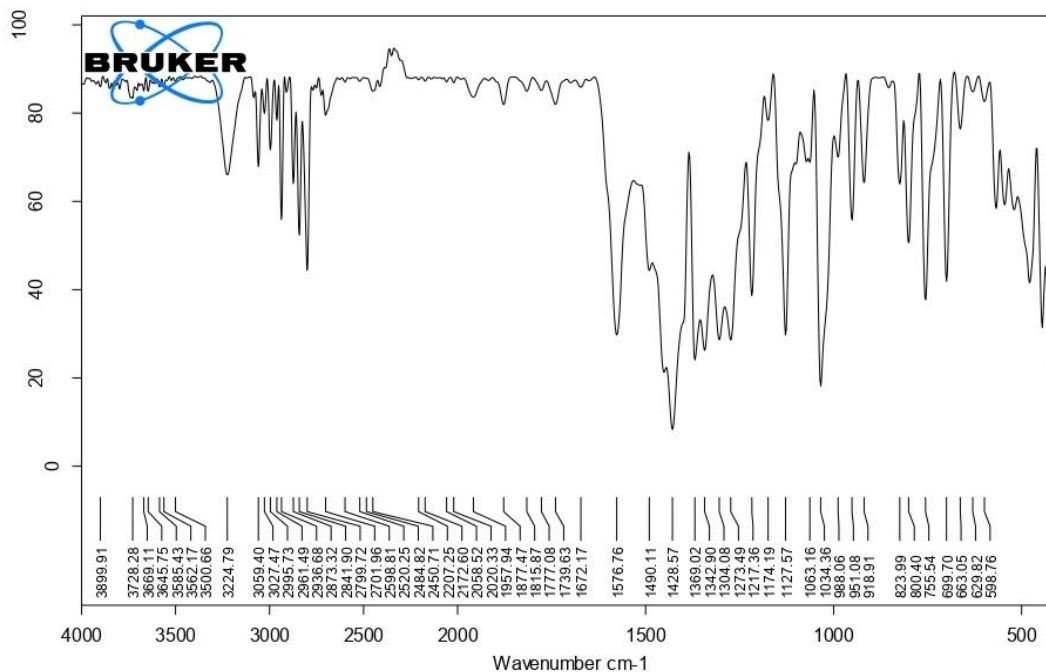


Figure (3): Calibration curve for the Estimation of Mirtazapine by using 0.1N Hydrochloric acid Buffer.

Table (5): Flow properties various formulations of SSEDDS (M1-Mcp).

Property	M1	M2	M3	M4	M5	M6	M7	M8	Mcp
Angle of repose (0)	30	27.3	26.3	22.1	18.2	19.1	14.3	16.1	25.64
Bulk density (gr/cc)	0.494	0.55	0.54	0.54	0.53	0.45	0.46	0.6	0.5
True density(gr/cc)	0.63	0.70	0.75	0.75	0.59	0.61	0.62	0.8	0.64
Carr's index (%)	22%	21.4%	28%	28%	10.16%	26.2%	25%	25%	21.87%
Hausner's ratio	1.28	1.27	1.43	1.38	1.11	1.35	1.33	1.33	1.28
Loading factor	0.18	0.16	0.16	0.15	0.13	0.12	0.14	0.15	0.12



A

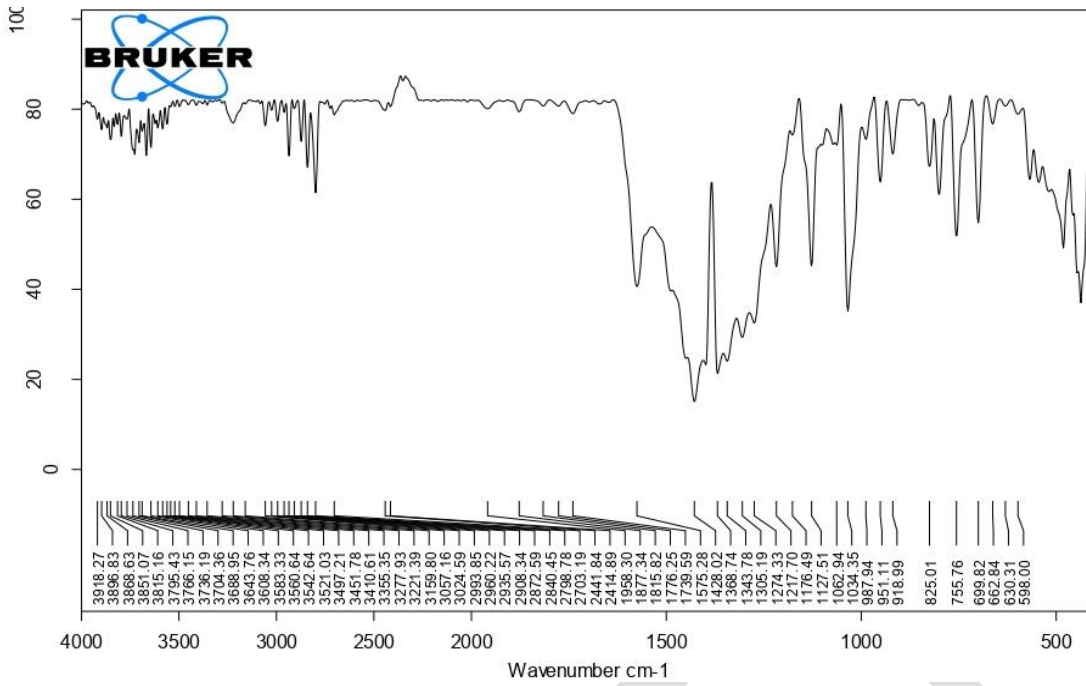


Figure (4): FTIR Spectrum of A. Pure drug B. Pure drug with Excipients.

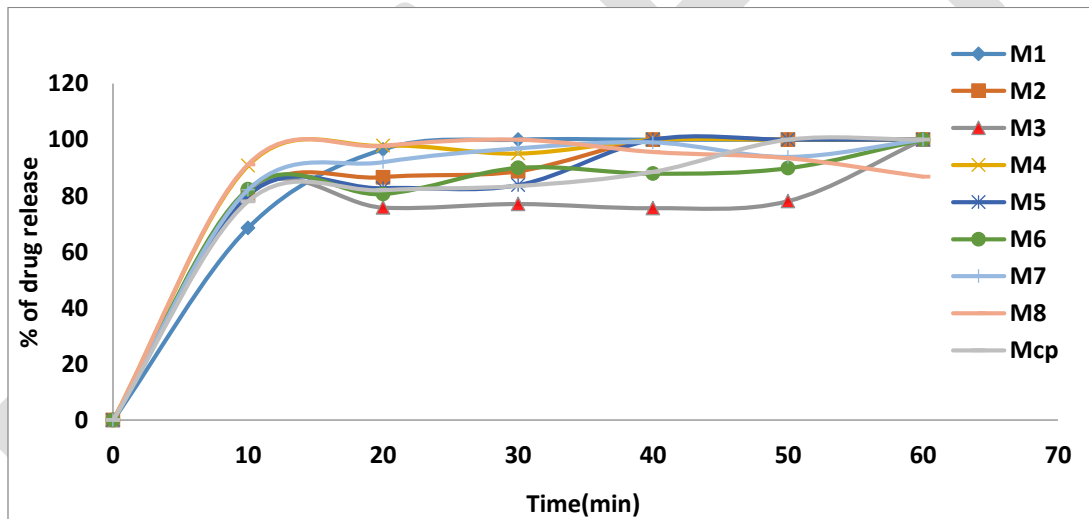


Figure (5): Mean Dissolution Profile of SSEDDS (±SD).

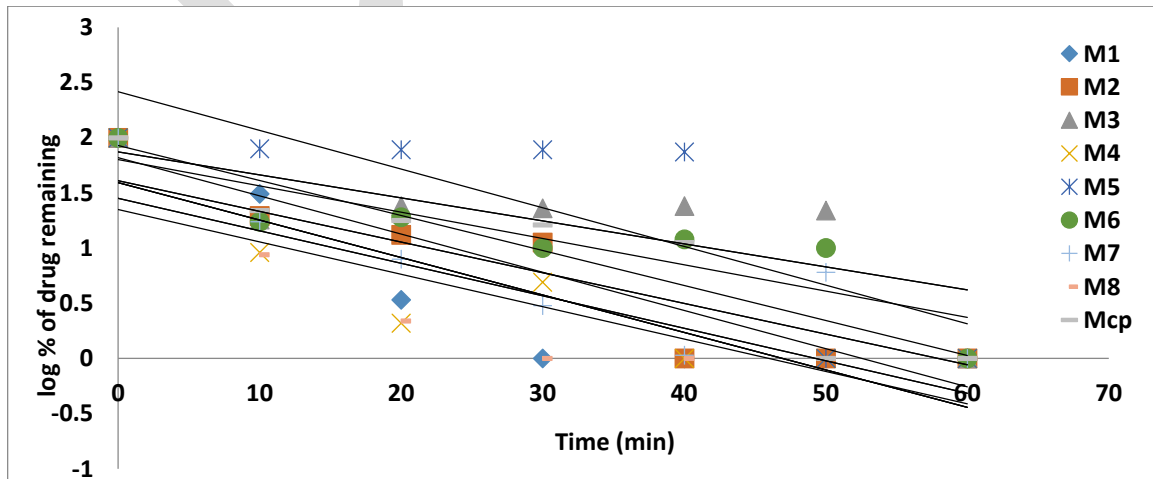


Figure (6): First orders Dissolution Profile of SSEDDS.

Table (6): Dissolution Parameters of prepared SSEDDS.

Formulation	T100(min)	T50(min)	‘r’(Correlation Coefficient)		K1	PD20
			Zero order	First order		
M1	30	8	0.7553	0.8777	0.221	96.57
M2	40	6.5	0.7592	0.9450	0.039	86.6
M3	60	13	0.7076	0.7476	0.027	75.8
M4	40	5.5	0.6695	0.8639	0.147	97.9
M5	40	25.5	0.8702	0.8739	0.00012	20.8
M6	60	12.5	0.7306	0.8730	0.009	80.64
M7	60	6	0.7076	0.8534	0.078	92.02
M8	30	20	0.6624	0.8348	0.064	97.80
MCP	50	11.5	0.7815	0.9349	0.020	81.99

Table (7): Stability studies of LSEDDS and SSEDDS for Emulsification, Phase separation, angle of repose and drug content after 3 Months (n=3).

Formulation	LSEDDS		SSEDDS	
	Emulsification Time (Min)	Phase Separation	Angle of repose(0)	Drug Content (%)
M1	<1	No	26	98.1
M2	<1	No	27.1	99.10
M3	<1	No	28.2	98.11
M4	<1	No	29.0	97.17
M5	<1	No	28.1	99.10
M6	<1	No	26.8	98.13
M7	<1	No	28.9	99.38
M8	<1	No	29.1	98.88
MCP	<1	No	29.9	99.10

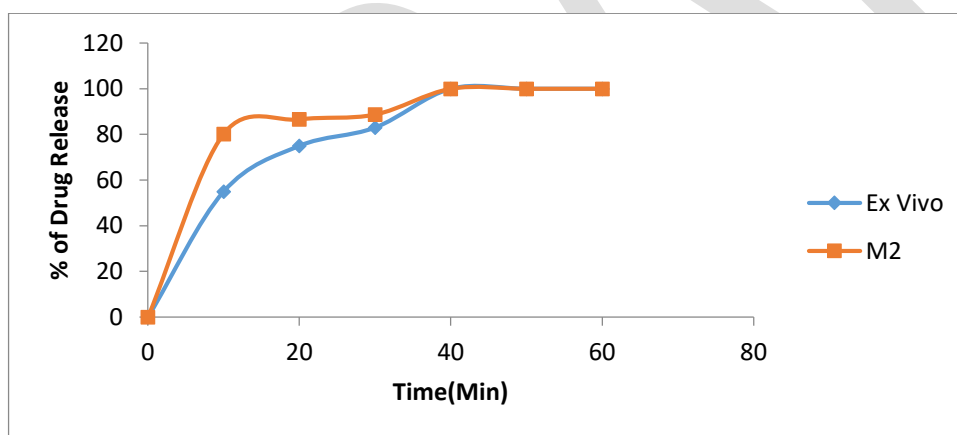


Figure (7): Comparison of Dissolution Profile of Ex Vivo (LSEDDS (M4) and SSEDDS (M2).

Table (8): Analysis of Variance of T100

Source	SS	df	MSS	F	p	Remarks
Model	6.68	7	0.9543	14.07	0.0051	Significant
A-Smix(Tween 80-PEG 400)	0.5875	1	0.5875	8.66	0.0321	
B-Speed	0.0569	1	0.0569	0.8394	0.4016	
C-Time	0.5875	1	0.5875	8.66	0.0321	
AB	3.40	1	3.40	50.07	0.0009	
AC	0.1300	1	0.1300	1.92	0.2249	
BC	1.86	1	1.86	27.49	0.0033	

ABC	0.0569	1	0.0569	0.8394	0.4016	
Residual	0.3392	5	0.0678			
Lack of Fit	0.3392	1	0.3392			
Pure Error	0.0000	4	0.0000			
Cor Total	7.02	12				

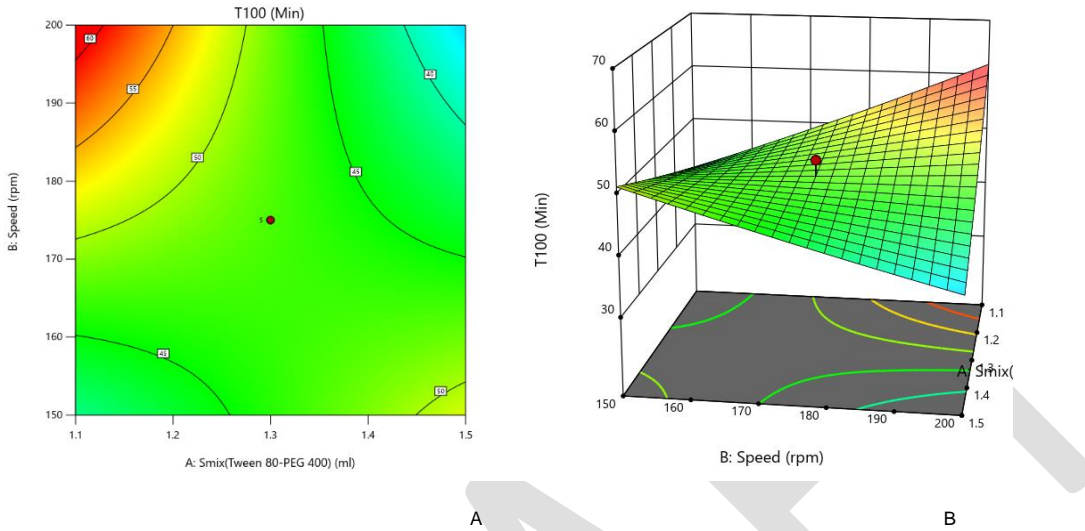


Figure (8): A. Counter plots of T100 B. 3D Surface Plots.

Table (9): Analysis of Variance of T50

Source	Sum of Squares	df	Mean Square	F-value	p	Remark
Model	6.98	7	0.9973	3367.53	< 0.0001	Significant
A-Smix(Tween 80-PEG 400)	0.1328	1	0.1328	448.50	< 0.0001	
B-Speed	0.1487	1	0.1487	502.23	< 0.0001	
C-Time	2.18	1	2.18	7368.30	< 0.0001	
AB	0.8163	1	0.8163	2756.24	< 0.0001	
AC	0.5241	1	0.5241	1769.76	< 0.0001	
BC	0.6252	1	0.6252	2111.14	< 0.0001	
ABC	2.55	1	2.55	8616.56	< 0.0001	
Residual	0.0015	5	0.0003			
Lack of Fit	0.0015	1	0.0015			
Pure Error	0.0000	4	0.0000			
Cor Total	6.98	12				

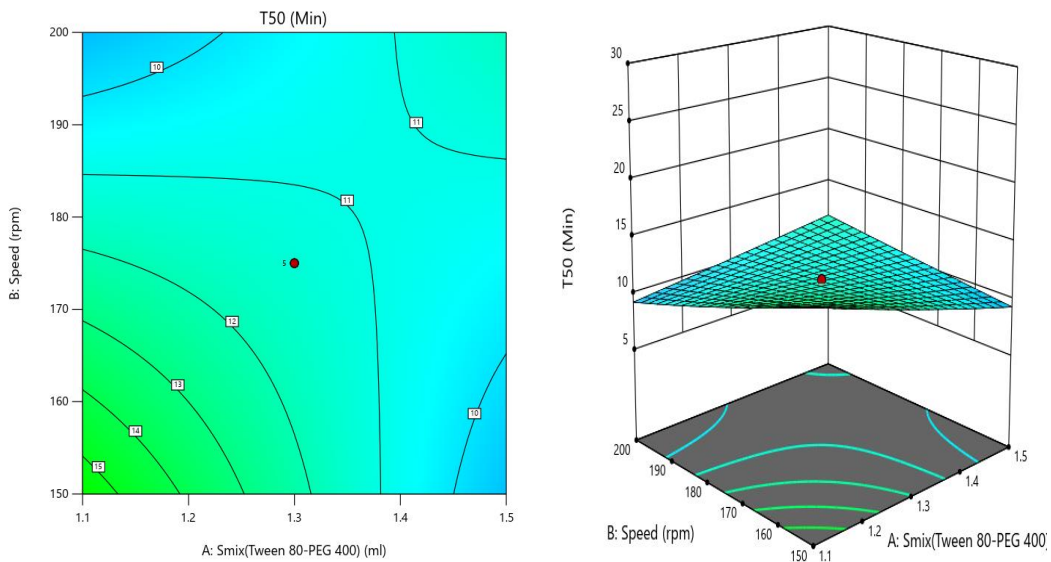


Figure (9): A. Counter plots of T50 B. 3D Surface Plots of T50

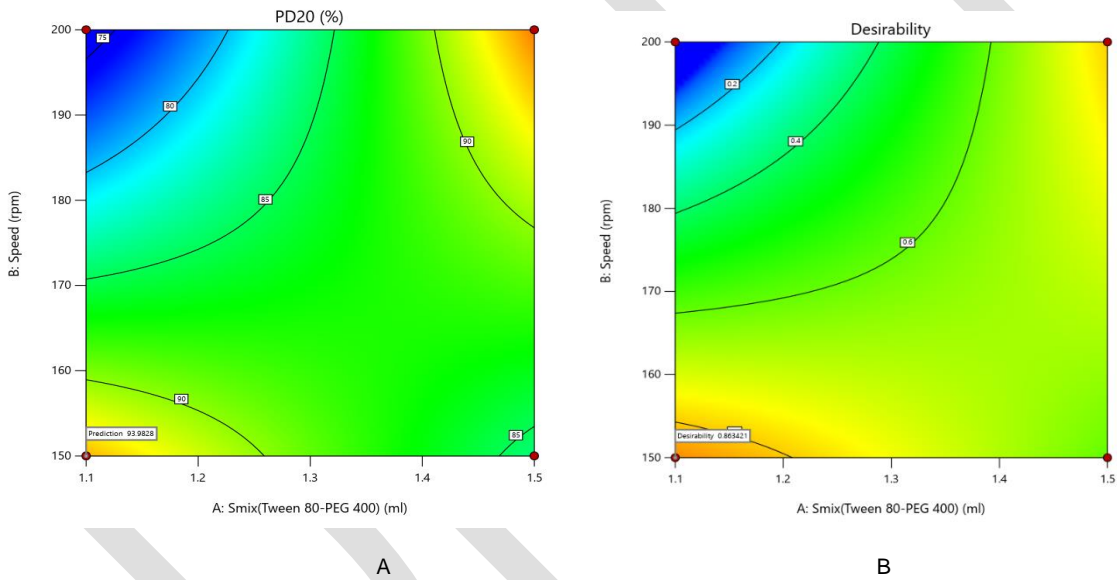
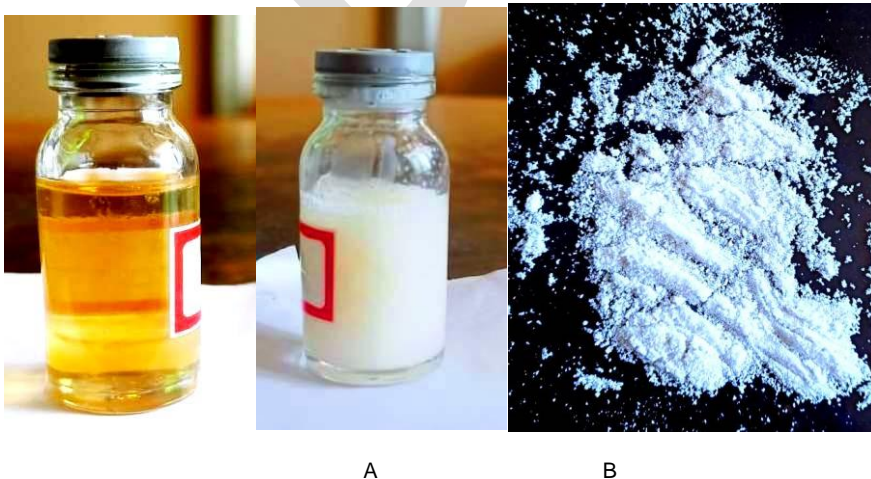


Figure (10): A. Counter Plot of Optimized PD20 B. Desirability Plot



A

B

C

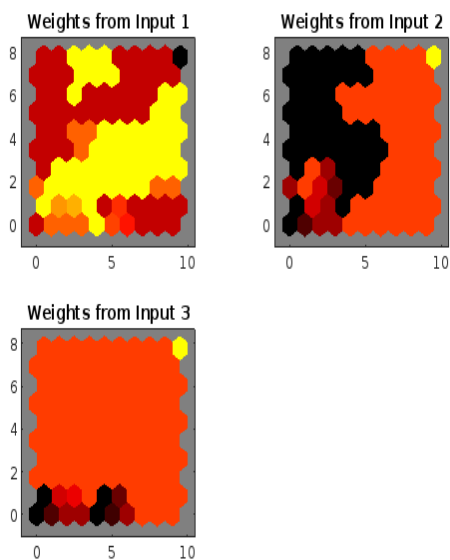
Figure (11): Optimized A.LSEDDS B. After dilution C.Solid state.

Table (10): Confirmation of the Results.

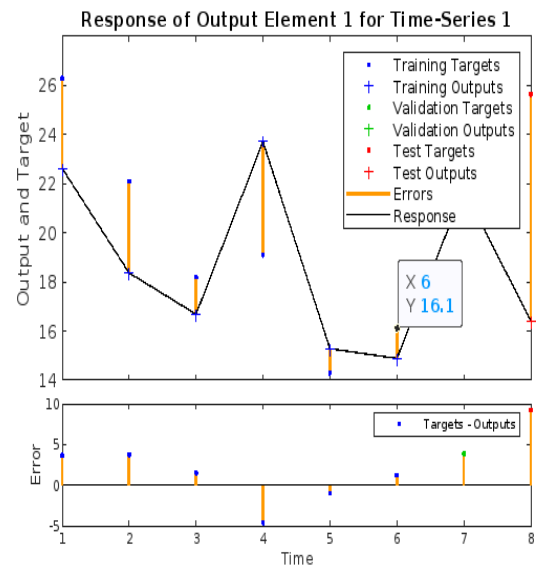
Solution 1 of 59 Response	Predicted Mean	Predicted Median*	Std Dev	95% CI low for Mean	95% CI high for Mean	95% TI low for 99% Pop	95% TI high for 99% Pop
T100†	31.4829	31.4151	2.9211	24.5874	39.2319	13.6256	56.5286
T50†	8.0481	8.0478	0.0976416	7.80507	8.29485	7.34637	8.78121
PD20†	93.9828	93.8197	5.5433	81.0698	108.952	60.8478	144.658

Table (11): R², Coefficient variance (CV %), Standard deviation and Adeq.Precision.

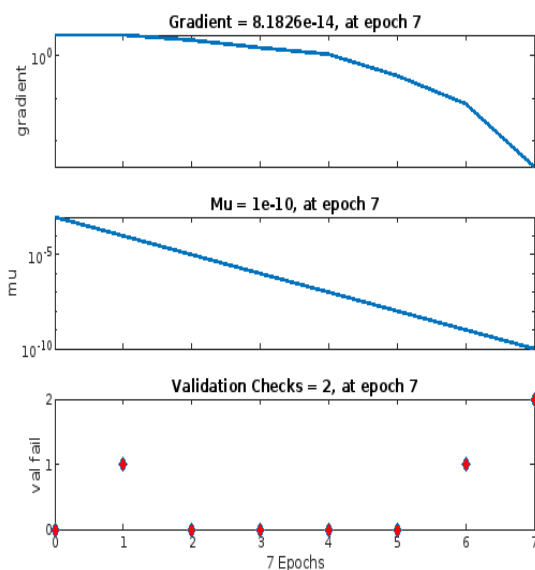
Response	R2	CV %	Std. Dev.	Adeq Precision
T100	0.9517	3.79	0.2604	11.1045
T50	0.9998	0.5117	0.0172	200.3358
PD20	0.7942	1.32	0.0256	5.5343



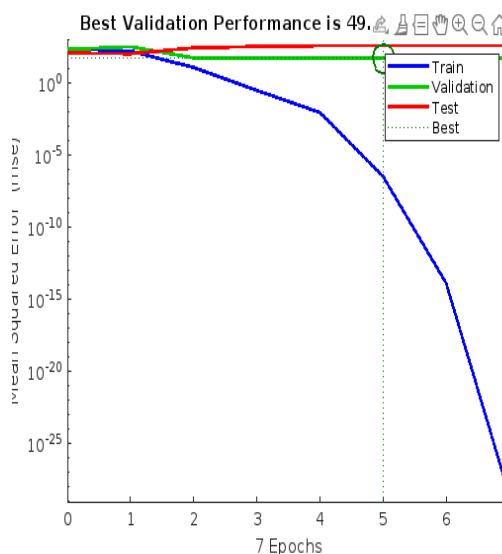
A. Weight planes plot



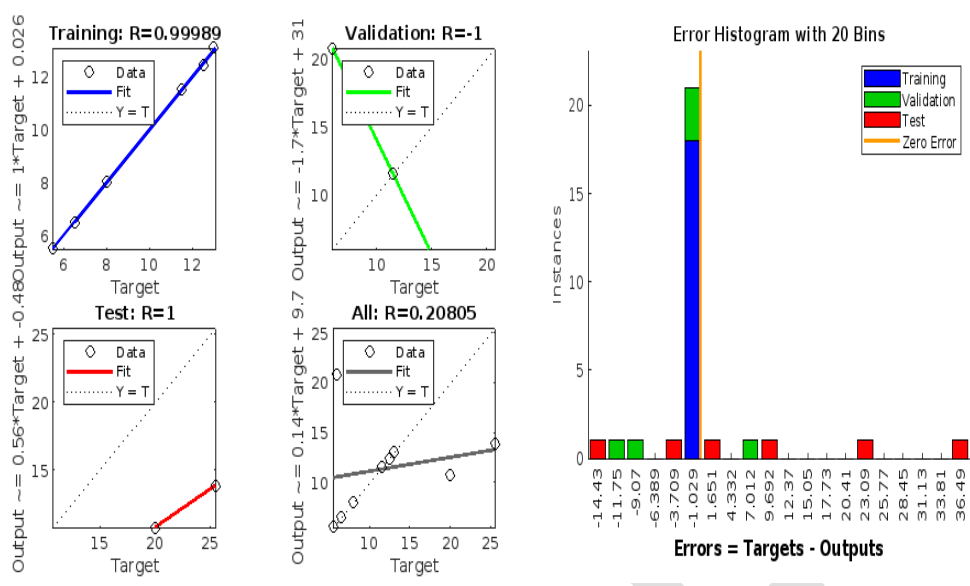
B. Response plot



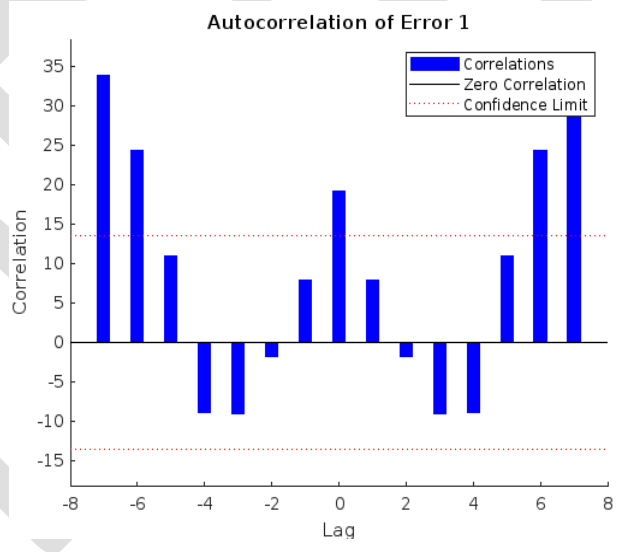
C. Training state plot



D. Performance Plot



E. Regression Plot F. Error histogram Plot



G. Error Auto correction Plot

Figure (12): Results of NNS modeling Levenberg-Marqardt learning method.

A. Weight planes plot B. Response plot C. Training state plot D. Performance Plot E. Regression Plot F. Error histogram Plot G. Error Auto correction Plot

Table (12): Analysis of Variance of PD2O.

Source	Sum of Squares	df	Mean Square	F-value	p-value	Remark
Model	0.0126	7	0.0018	2.76	<0.1410	Significant
A-Smix(Tween 80-PEG 400)	0.0008	1	0.0008	1.20	0.3233	

B-Speed	0.0008	1	0.0008	1.17	0.3290	
C-Time	0.0000	1	0.0000	0.0403	0.8488	
AB	0.0048	1	0.0048	7.32	0.0425	
AC	0.0003	1	0.0003	0.4450	0.5343	
BC	0.0041	1	0.0041	6.33	0.0535	
ABC	0.0018	1	0.0018	2.80	0.1554	
Residual	0.0033	5	0.0007			
Lack of Fit	0.0033	1	0.0033			
Pure Error	0.0000	4	0.0000			
Cor Total	0.0159	12				

Table (13): Entrapment Efficiency &CP of formulations

Formulation	M1	M2	M3	M4	M5	M6	M7	M8	MCP
EE(%)	81.22	83.44	84.11	85.15	85.336	87.12	88.54	87.10	81.90
CP(°C)	61.2	63.8	69.11	68.90	66.23	65.18	69.10	68.98	67.12