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FORMULATION AND EVALUATION OF SOLID SELF EMULSIFYING DRUG DELIVERY SYSTEM FOR DRUG MIRTAZAPINE

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Keywords:

Mirtazapine, SEDDS, Zeta potential, *In-vitro* release studies and Stability studies

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ABSTRACT: Objective: In the present dissertation work, the aim was to prepare self-emulsifying drug delivery systems (SEDDS) of mirtazapine to improve its solubility with a view to enhance its oral bioavailability. **Methods:** The prepared SEDDS was the concentrate of the drug, oil-Capmule MCM EP, surfactant tween 80 and PEG 400 as a co-surfactant. The optimized microemulsion was converted into solid form by adsorption technique by using as Neusiline US2 solid carrier. The formulation was evaluated for various tests such as solubility, drug content, emulsification time, phase separation study, dispersibility test, droplet size analysis and PDI determination and zeta potential and *in-vitro* release study, and *in-vitro* permeation study. **Results:** The optimized formulation F5 showed drug release (96.97 ± 1.89), droplet size (153), Zeta potential (-30mv). All formulations of mirtazapine SEDDS were showed faster dissolution than plain drug, mean bioavailability of mirtazapine increase in respect to the plain drug. The F5 can be further used for the preparation of various solid SEDDS. In conclusion, self-emulsifying drug delivery system has become promising tool to overcome shortcomings associated with conventional delivery.

INTRODUCTION: The oral route is the most preferred route of drug delivery for the treatment of number of diseases. Nearly 35 to 40% of newly launched drugs possess low aqueous solubility which leads to their poor dissolution and thereby low bioavailability, resulting in high intra and inter-subject variability & lack of dose proportionality. For these drugs absorption rate from the gastro-intestinal tract is mainly governed by dissolution & improvement in solubility may lead to enhance bioavailability. There is number of techniques to overcome such problems arising out of low solubility & bioavailability, which may result in improved therapeutic efficacy of these drugs.

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The techniques like complex formation with cyclodextrin, solid dispersion, liposome formation, co-precipitation, micronization, salt formation, use of micelles, co-grinding & emulsification had been used for improving the dissolution of drugs with low solubility.

Recently, a new technique self Emulsifying Drug Delivery System (SEEDS) has been developed to enhance the solubility of the drug. SEDDS are defined as isotropic mixtures of natural or synthetic oils, solid or liquid surfactants or alternatively, one or more hydrophilic solvents & co-solvents [2, 3].

Mechanism of Self Emulsification: [2, 3] Self-emulsifying processes are related to the free energy, ΔG given by;

$$\Delta G = \Sigma N \pi r2 \sigma$$

Where,
N = Number of droplets with radius r
Σ = Interfacial energy

It is apparent from the above equation that spontaneous formation of an interface between oil & water phase is not favorable due to higher energy level. The system commonly classified as SEDDS has not yet been shown to emulsify spontaneously in true thermodynamic sense.

Groves & Mustafa developed a method of quantitatively assessing the ease of emulsification by monitoring the turbidity of oil-surfactant system in aqueous system, using phosphate nonyl-phenoxylate (PNE) & phosphate fatty alcohol ethoxylate (PFE) in n-hexane & suggested that emulsification process may be associated with the ease with which water penetrates the oil-water interface, with formation of liquid crystalline phase resulting in swelling at interface, thereby resulting in greater ease of emulsification. Pouton has said that the emulsification capacities of surfactant may be related to phase inversion behavior of the system. If one increases the temperature of the oil in the water system which is stabilized by using non-ionic surfactants, the cloud point of the surfactant will be reached followed by phase inversion.

The surfactant is highly mobile at phase inversion at phase inversion temperature due to which o/w interfacial energy required for emulsification.

Pouton has suggested that the specificity combination required to allow spontaneous emulsification is associated with a minimization of phase inversion temperature, thereby increasing the ease of emulsification. For a system having co-surfactants, separation of components between the oil & aqueous phases may take place leading to a mechanism described as "Diffusion & standing" whereby the oil is solubilized, leading to migration into the aqueous phase.

Lipid Formulation Classification System: [1, 3, 4]

TABLE 1: THE LIPID FORMULATION CLASSIFICATION SYSTEM [1]

Formulation Type	Materials	Characteristics	Advantages	Disadvantages
Type I	Oils without surfactants (*e.g.* tri-, di-and monoglycerides)	Non dispersing requires digestion	GRAS status; simple; excellent capsule Compatibility	Formulation has poor solvent capacity unless drug is highly lipophilic
Type II	Oils and water-insoluble surfactants	SEDDS formed without water-soluble component	Unlikely to lose solvent capacity on dispersion	Turbid o/w dispersion (particle size 0.25-2µm)
Type III	Oils, surfactants, Co-solvents/ Co-surfactant (both water-insoluble and water-soluble excipients)	SEDDS/SMEDDS are formed with water-soluble components	Clear or almost clear dispersion; drug absorption without digestion	Possible loss of solvent capacity on dispersion.
Type IV	Water-soluble surfactants and cosolvents / cosurfactants (no oils)	Formulation disperses typically to form a micellar solution	Formulation has good solvent capacity for many drugs	Likely loss of solvent capacity on dispersion; may not be digestible

Solid SEDDS (S-SEDDS): [5, 6, 7] SEDDS can exist in either liquid or solid states. However, SEDDS are usually limited to liquid dosage forms because many excipients used in SEDDS are not solids at room temperature. In the 1990s, S-SEDDS were usually in the form of self-emulsifying (SE) capsules, SE solid dispersions and dry emulsions, but other solid SE dosage forms have emerged in recent years, such as SE pellets/tablets, SE beads, microspheres/nanoparticle and SE suppositories/ implants.

Solidification techniques for transforming liquid/ semisolid SEDDS to S-SEDDS.

1. Capsule filling with liquid and semisolid self-emulsifying formulations
2. Spray drying
3. Freeze drying
4. Adsorption to solid carriers
5. Melt granulation
6. Melt extrusion/extrusion spheronization

MATERIALS AND METHODS: Mirtazapine was obtained as a gift sample from Mylon Laboratories LTD Hyderabad, India. CAPMUL MCM EP was gifted by ABITEC CORP. USA PEG 400 and Tween 80 obtained from MOHINI ORGANICS PVT.LTD and NEUSILIN US2 by FUJI CH EMICAL, JAPAN.

All other chemicals were of reagent grade.

Preparation of Liquid SEDDS: [8] The formulation of Liquid Self-Emulsifying drug delivery system was carried out by simply using in magnetic stirrer. In this technique first drug was solubilized in the mixture of surfactant and co-surfactant at 40 °C. Then oil was added dropwise using a magnetic stirrer at 40-50 °C. The formed a mixture was stored on the magnetic stirrer for nearly 15 to 20 min.

Evaluation of Liquid Self Emulsifying Drug Delivery System: [9, 8]

Emulsification Time: [9]

Procedure: Determine the emulsification time of SEDDS according to United State Pharmacopeia dissolution II apparatus. Add dropwise 0.5 ml of each formulation into 500 ml of purified water at 37 ºC. Provide gentle agitation by a standard stainless steel dissolution paddle rotating at 50 rpm. Assess the emulsification time visually.

Phase Separation Study: [9]

Procedure: Each Liquid SMEDDS formulation 100mg was added to 100 ml volumetric flask and diluted with distilled water up to the mark. After inverting volumetric flask for 3-4 times, each mixture was stored for 2 h and phase separation was observed visually.

Drug Content: [10, 11]

Procedure: Prepared Liquid SMEDDS containing Mirtazapine equivalent to 10 mg was added in 100 ml volumetric flask containing methanol and mixed it well. Then from this appropriate amount of solution was taken out and diluted appropriately with methanol and drug content was determined using UV- spectrophotometer at λ_{max} 315 nm.

Dispensability Test: [10, 11] The efficiency of self-emulsification of oral nano or microemulsion can be determined by using a standard USP II dissolution apparatus. In this add 1ml of the formulation to 500 ml of water maintained at 37 ± 0.5 °C in the dissolution apparatus. Provide gentle agitation by standard stainless steel dissolution paddle rotating at 50 rpm. Assess the in vitro performance of the formulation using the following grading systems.

- **Grade A:** Rapidly forming micro-emulsion, having a clear or bluish appearance.
- **Grade B:** Rapidly forming a slightly less clear emulsion having the bluish-white appearance.
- **Grade C:** Fine milky emulsion formed within 2 min.
- **Grade D:** Dull greyish white having a slightly oily appearance that is slow to emulsify.
- **Grade E:** Formulation exhibiting either poor or minimal emulsification with large oil globules present on the surface.

***In-vitro* Drug Release Study of the Prepared Liquid Self-Emulsifying Drug Delivery System:** [9, 10, 11] Mirtazapine is BCS class II drug that has low solubility. In this study, the liquid SEDDS was filled in the sac prepared by the eggshell. The formulation which contains 15 mg Mirtazapine of was added in each sac. The temperature conditions were maintained as per IP. Here also USP dissolution apparatus II was used. The speed of the paddle was adjusted to 75 rpm. The Aliquots of the samples were collected from the dissolution apparatus at fixed interval. The equivalent amount of fresh medium was added to the dissolution apparatus after each collection of the aliquot to maintain the sink conditions.

The UV absorbance was measured to calculate the amount of drug Diffused from the egg sack after each time interval. This study gives the effect of Self-Emulsifying formulation on the permeability characteristics of Mirtazapine.

Droplet Size Analysis and PDI Determination and Zeta Potential: Size analysis of micro-emulsion was carried out by dynamic light scattering with Zetasizer HAS 3000. The sample was placed in square glass cuvettes and droplet size analysis was carried out for optimized

microemulsion formulations. The optimized micro-emulsion formulation was diluted with the (100 times) water and then the particle size of the system was determined. Zeta potential of microemulsion was carried out by dynamic light scattering with Zetasizer HAS 3000. The sample was placed in the clear Zeta cells and results were recorded.

Preparation of Solid SEDDS: The method used for S-SEDDS was Adsorption carrier method. For the preparation of solid SEDDS, the optimized formulation of liquid SEDDS which passed all these evaluation parameters are selected. Then this liquid SEEDS containing Mirtazapine was added drop-wise over the solid adsorbent Neusiline US2 contained in a porcelain dish in 1:1 proportion. After each addition the mixture was homogenized using glass rod to ensure uniform distribution of the formulation.

The resultant mass was passed through sieve no. 65 at ambient temperature and stored until further use.

Solid-State Characterization of Solid SEDDS:

Bulk Density and Tapped Density: Bulk density and tapped density were measured using 10 ml graduated measuring cylinder by tapping method. Bulk density and tapped density were calculated by following formula

$$\text{Bulk Density} = \text{Mass of powder} / \text{Bulk Volume}$$

$$\text{Tapped Density} = \text{Mass of powder} / \text{Tapped Volume}$$

Angle of Repose (θ): This is the maximum angle possible between the surface of a pile of powder or granules and the horizontal plane. The granules were allowed to flow through the funnel fixed to a stand at definite height (h). The angle of repose was then calculated by measuring the height and radius of the heap of granules formed.

$$\theta = \tan^{-1} (h/r)$$

Compressibility Index: The compressibility of the granules was determined by Carr's Compressibility Index.

$$\text{Carr's compressibility index (\%)} = TBD - LBDTBD \times 100$$

Hausner Ratio: A similar index like compressibility index has been defined by Hausner. Hausner ratio can be calculated by the formula:

$$\text{Hausner ratio} = TBD / LBD$$

Differential Scanning Calorimetry (DSC): The molecular state of the drug in S-SEDDS formulation was evaluated by performing a DSC analysis of S-SEDDS. The samples (about 3.00 mg) were placed in standard aluminum pans, and dry nitrogen was used as effluent gas. All samples were scanned at a temperature speed of 5 °C/min and the heat flow from 0 to 150 °C.

X-ray Powder Diffraction: The XRD patterns of pure drug and S-SEDDS formulation were obtained using X-ray diffractometer. The measuring conditions were as follows: CuKα radiation, nickel filtered; graphite monochromator; 45 kV voltage; and 40 mA current with X'celerator detector.

Morphological Analysis of S-SEDDS by SEM: The surface morphology of the pure drug and S-SEDDS formulation was investigated by scanning electron microscope (SEM). Samples were fixed on a brass stub using the double-sided adhesive tape and were made electrically conductive by coating with a thin layer of gold and SEM images were recorded at 10 kev accelerating voltage.

RESULT AND DISCUSSION:

Solubility Determination of Mirtazapinein Different Oils: Solubility studies clearly indicated that amongst the various oily phases that were screened, Mirtazapine showed maximum solubility in Capmul MCM EP (85.57 ± 0.22 mg/ml). Capmul MCM EP had a good solvent capacity for drug. Further Capmul MCM EP had good aqueous solubility which may help in easy dispersion of drug in aqueous medium. From the solubility study we selected Capmul MCM EP.

TABLE 2: SOLUBILITY OF MIRTAZAPINEIN DIFFERENT OILS

S. no.	Oils	Concentration (mg/ml)
1	Capmul MCM EP	85.57 ± 0.22
2	Oleic Acid	50.15 ± 0.35
3	Soyabean oil	55.31 ± 0.43
4	castor oil	27.96 ± 0.76
5	Olive oil	14.89 ± 0.68

Solubility of Mirtazapine in Different Surfactants and Co-Surfactants: Among the surfactants and co-surfactants tested, Tween 80 had shown maximum solubility of 69 mg/ml and PEG 400 had shown solubility of 84.8 mg/ml. Therefore, Tween 80 and PEG 400 were selected as surfactant and co-surfactant respectively.

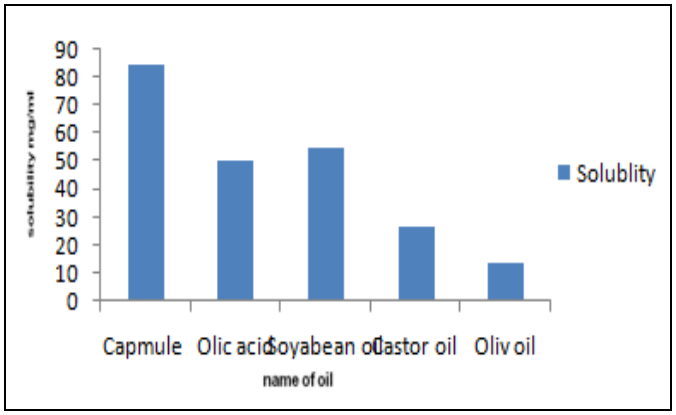

FIG. 1: SOLUBILITY OF MIRTAZAPINE IN DIFFERENT OILS

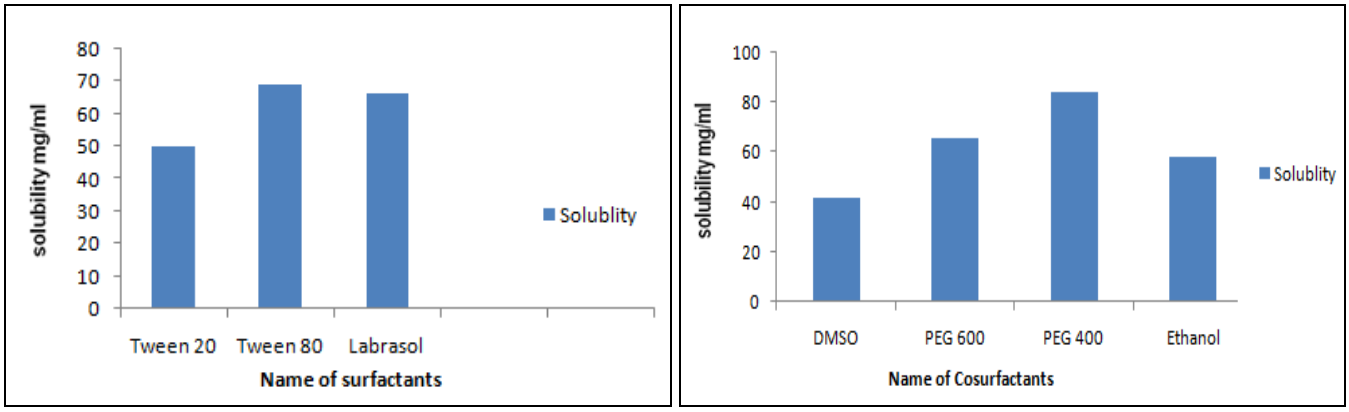

FIG. 2: SOLUBILITY OF MIRTAZAPINE IN DIFFERENT SURFACTANTS AND CO-SURFACTANTS

TABLE 3: SOLUBILITY OF MIRTAZAPINE IN DIFFERENT SURFACTANTS AND CO-SURFACTANTS

S. no.		Surfactant	Solubility (mg/ml)
1	Surfactants	Tween 20	50.15 ± 0.26
2		Tween 80	69 ± 0.53
3		Labrasol	66.56 ± 0.39
4	Co-surfactants	DMSO	42.25 ± 0.34
5		PEG 600	66.26 ± 0.81
6		PEG 400	84.8 ± 0.57
7		Ethanol	58.96 ± 0.76

Construction of Pseudo-Ternary Phase Diagrams: From ternary phase diagram it was observed that there was slight increase in microemulsion region as the ratio of surfactant to co-surfactant was increased. The difference between micro emulsifying areas of all three ternary diagrams was slight. From the observation it was found that microemulsion with higher oil percent was turbid and unstable. In the present study, three S/CoS ratio, 1:1, 2:1 3:1, were tried and phase diagrams were observed for the maximum microemulsion region and also having good flow property. It can be concluded that 3:1 proportion of surfactant and co-surfactant required getting optimum concentration of oil. Moreover, since the drug is lipid-soluble, oil concentration is important factor to entrap required amount of drug dose. 3:1 ratio of S/CoS was selected for further study.

Composition of Oil, Surfactant and Co-Surfactant (S-CoS mix):

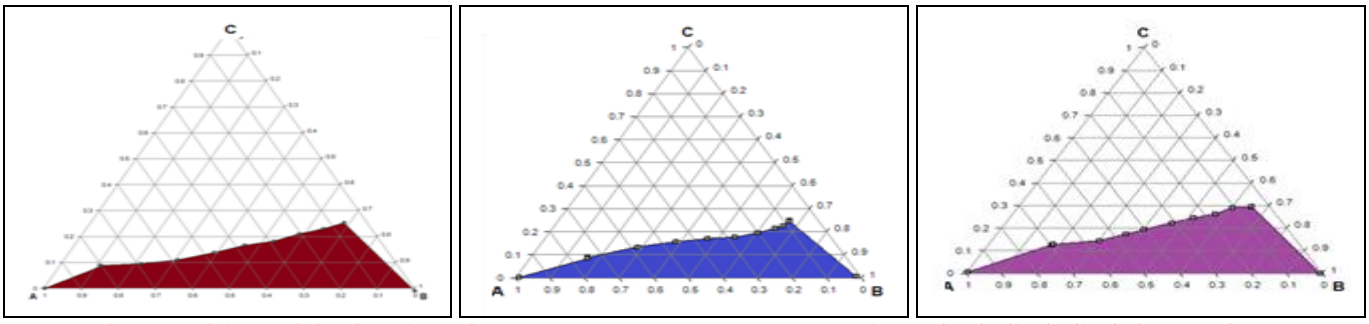

FIG. 3: PHASE DIAGRAM OF CAPMULE MCM, TWEEN 80 + PEG 400 (1:1), (2:1), (3:1) AND WATER

Drug Excipient Interaction:

UV Scan Analysis: The compatibility study was performed on UV spectrophotometer at initial, second week and fourth week. The scanning values were found in the range of 312 to 313 nm. Microemulsion without drug is not showing any absorption maximum at 313 nm. There was no significant variation in the λ-max of microemulsion with drug as compared to pure drug. This indicates no drug excipient interaction.

Compatibility Study by IR Spectra: FTIR spectra of drug with excipients are shown below. The prominent peak of mirtazapine showed that there was no incompatibility between mirtazapine and excipients.

TABLE 4: COMPATIBILITY STUDY

S. no.	Drug + Excipient	λ max (nm)		
		Initial	2 weeks	4 weeks
1	Mirtazapine + Tween 80	312	313	313
2	Mirtazapine + Capmule MCM	313	313	312
3	Mirtazapine + PEG 400	313	312	314

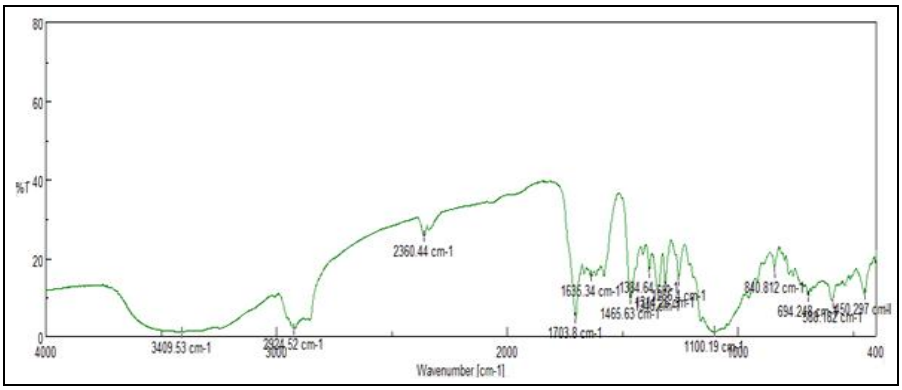

FIG. 4: IR SPECTRA OF DRUG

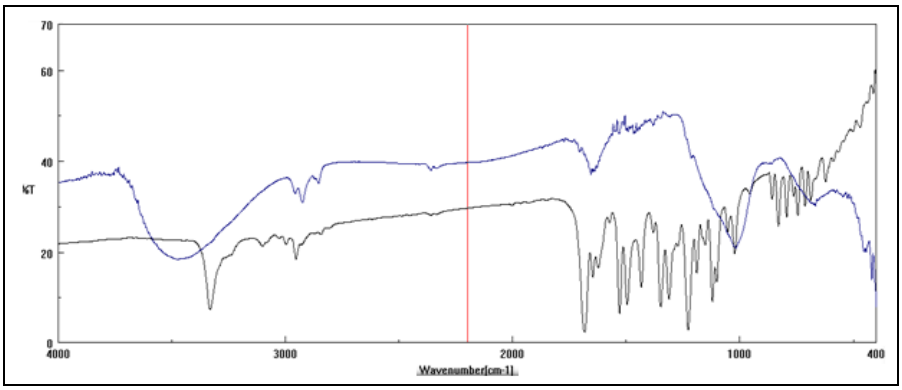

FIG. 5: FTIR SPECTRA; A: PURE DRUG, B: NEUSILIN

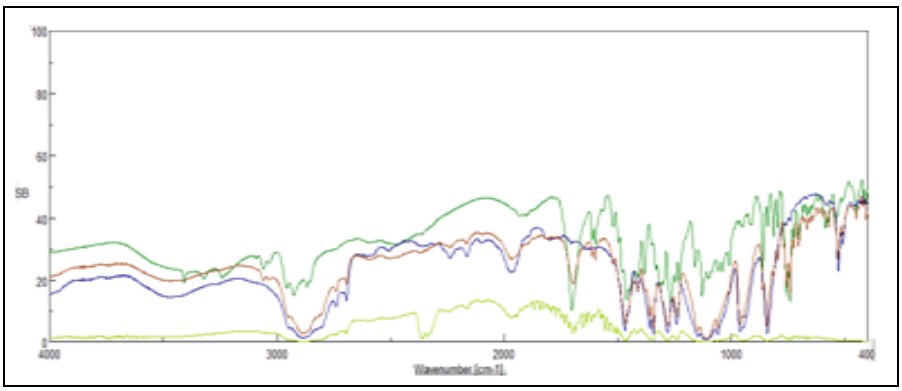

FIG. 6: FTIR SPECTRA; A: CAPMULE MCM EP, B: TWEEN 80, C: PEG 400, D: FORMULATION

The Procedure for Formulation of Liquid and Solid SEDDS:

Preparation of Self-Emulsifying Drug Delivery System (SEDDS): The emulsified area was low at all other Km values (1:1, 2:1) because Tween 80 was one of the hydrophilic surfactant (HLB 14), with area of o/w microemulsion system was small. In contrast, at the ratio of 3:1 the low concentration of co-surfactant reduced the fluidity of interfacial film which consequently, decreased the solubility of oil in water and microemulsion existence region. Amount of water in the system determine consistency of microemulsion system which was highly viscous and the viscosity of the system goes on increasing as increase in water content. Thus highly viscous and clear microemulsion gel was obtained and drug release from microemulsion was slow.

TABLE 5: PERCENTAGE COMPOSITION OF OIL, SURFACTANT, CO-SURFACTANT OF SELECTED SEDDS

S. no.	Formulation code	Drug (mg)	% Composition (w/v)		
			Oil (ml)	Tween 80 (ml)	PEG 400 (ml)
1	F1	300	2	3	1
2	F2	300	2	3.2	1.3
3	F3	300	2	4.5	1.5
4	F4	300	3.5	3	1
5	F5	300	3.5	3.2	1.3
6	F6	300	3.5	4.5	1.5
7	F7	300	5	3	1
8	F8	300	5	3.2	1.3
9	F9	300	5	4.5	1.5

Evaluation of Self-Emulsifying Drug Delivery System of Mirtazapine:

Emulsification Time: Transmittance study revealed that as the concentration of surfactant increases the transmittance of resulting emulsions increases. The ease of emulsification or rate of emulsion formation was measured by UV-spectrophotometer **Table 6**.

If the concentration of oil increases, the transmittance as well as the ease of emulsification decreases it may be due to increase in globule size of oil. Also system with low surfactant/co-surfactant ratio unable to decrease the surface tension between oil phase and aqueous phase up to the level at which microemulsion can be formed spontaneously.

Phase Separation Study: All formulations were stable for two hours in distilled water. No phase separation occurred for any formulation. Hence, all the formulations were subjected for further evaluation.

TABLE 6: EMULSIFICATION TIME, PHASE SEPARATION & % DRUG CONTENT, DISPERSIBILITY TEST OF L-SMEDDS

Formulation code	Emulsification Time in sec	Phase separation	Drug content (%)	Dispersibility test
F_1	62	No	92.8	B
F_2	66	No	96.7	A
F_3	61	No	96.1	A
F_4	63	No	95.7	A
F_5	56	No	98.6	A
F_6	63	No	96.5	B
F_7	62	No	93.8	B
F_8	62	No	97.5	A
F_9	59	No	95.3	B

Drug Content Determination: Drug content of all formulations was found to be between 92.5-98.8%. Drug shows much more solubility in surfactant co-surfactant ratio than oil percent. And in F1 and F7 batches the surfactant co-surfactant percent is less than the other batches so they give less drug content (below 95%) as compared with the other batches. Formulation F_5 showed highest drug content (98.8%).

Dispersibility Test: The efficiency of self-micro emulsifying drug delivery system was also examined by the use of the dispersibility test. Grade A and Grade B formulation remained as

micro-emulsion when dispersed in the GIT. Table no. 32 gives a detailed account of the Dispersibility results of the various batches of the formulation of the Mirtazapine.

***In-vitro* Dissolution Study:** Drug release from the SEDDS formulation F_5 was found to be significantly higher as compared to other formulations.

In the observation table, we observe that F_1 and F_5 showed better drug release than other formulations which indicate as the oil percent increased drug release decreased. If we increase surfactant to cosurfactant ratio while keeping oil percent constant drug release increased. The reason behind this is as the oil percent increases the resultant globule size is more and this lead to the decrease in effective surface area for drug transfer into the aqueous phase. As surfactant to cosurfactant ratio increased the globule size of resultant system is less which means high effective surface area and faster drug transfer from oil phase to aqueous phase.

In F5 batch the quantity of oil is less than the surfactant co-surfactant ratio; in this both the oil and surfactant co-surfactant ratio is beneficial to drug release so that dug release is more from this formulation as compared to other formulation.

TABLE 7: OBSERVATION TABLE FOR IN VITRO DISSOLUTION OF LIQUID SEDDS MEAN ± S.D. (N=3)

Time (Min)	F_1	F_2	F_3	F_4	F_5	F_6	F_7	F_8	F_9
10	17.3	14.05	14.94	14.94	14.63	15.38	17.3	14.63	16.42
	±1.45	±1.46	±1.73	±1.28	±1.61	±1.38	±1.28	±1.79	±2.39
20	48.79	25.03	28.30	28.01	28.89	30.53	45.08	30.22	41.67
	±1.85	±1.61	±1.49	±1.61	±1.89	±1.47	±1.37	±1.64	±1.48
30	69.94	39.39	52.49	54.12	40.33	45.11	66.34	45.09	55.92
	±1.93	±1.82	±1.30	±2.27	±1.37	±49	±1.79	±1.82	±1.93
40	86.73	56.59	68.05	70.73	65.84	67.84	77.01	56.71	69.29
	±1.64	±1.72	±1.29	±1.76	±1.79	±1.56	±1.86	±1.74	±1.36
50	90.35	74.26	80.51	82.33	80.28	78.08	88.68	72.31	75.31
	±1.41	±1.21	±1.43	±1.72	±1.54	±1.48	±1.62	±2.24	±1.18
60	93.43	85.35	94.18	92.35	96.37	88.29	92.04	81.3	87.13
	±1.42	±1.36	±1.37	±2.38	±1.78	±1.25	±1.39	±2.19	±1.54

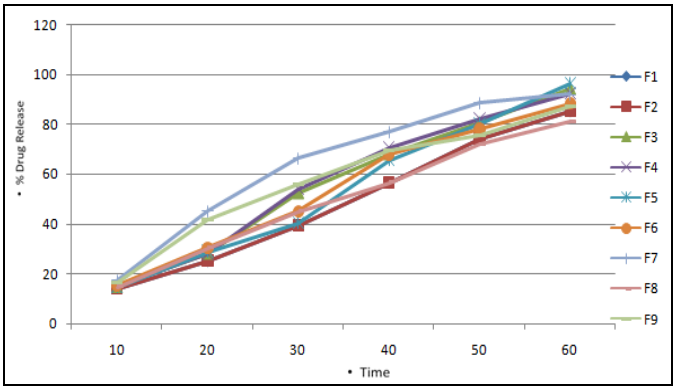

FIG. 7: DISSOLUTION PROFILE OF LIQUID SEDDS

Droplet Size Analysis and PDI Determination and Zeta Potential: The F5 batch was optimized as it gives the droplet size up to 153 nm the result also reveals that formulation shows less particle size this could be explained by the stabilization of the oil droplets as a result of the localization of the surfactant molecules at the oil-water interface.

Poly-dispersibility is the ratio of the standard deviation to the mean droplet size. This signifies the uniformity of droplet size within the formulation. The electrostatic forces of microemulsion droplets are critical for assessing the stability of SEDDS formulation. An increase in the electrostatic forces between microemulsion droplets and a decrease of electrostatic repulsive forces will result in the phase separation.

The surfactant Tween 80 and the Co-surfactant PEG 400 used in the study are non-ionic which do not contribute to the charge on the microemulsion. The charges on the microemulsion do not affect the stability of the microemulsion. The zeta potential and the droplet size were determined of F5batch which is better as compared to the other batches. The results are as follows:

TABLE 8: DROPLET SIZE, PDI ZETA POTENTIAL OF OPTIMIZED BATCHES

S. no.	Batch	Droplet size (nm)	PDI	Zeta potential
1	F5	153	0.25	-32mv

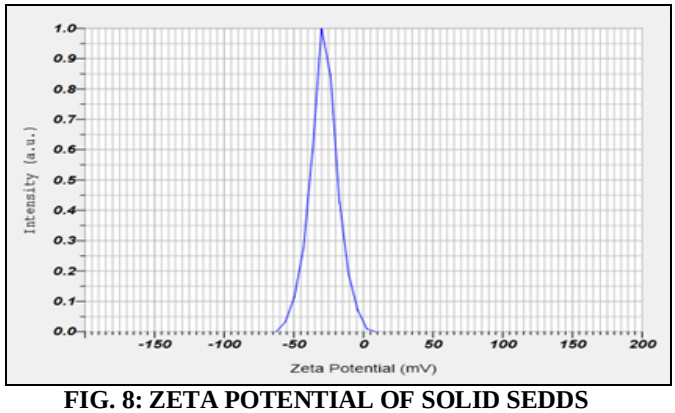

FIG. 8: ZETA POTENTIAL OF SOLID SEDDS

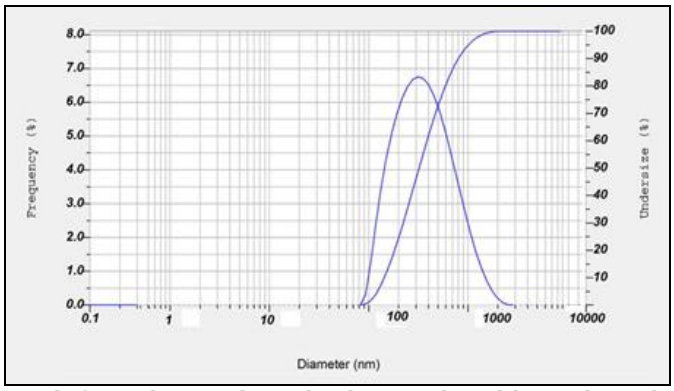

FIG. 9: DROPLET SIZE OF OPTIMISED SOLID-SEDDS

Factorial Design with Surface Plot and Optimization of Process Variables: The % drug release from the 9 batch experiments were used generate predictor equations for Mirtazapine with the independent variable as Oil Concentration (A) and Sur-CoS mix Ratio (B). The results of multiple regression analysis of variance test (ANOVA) are summarized in table. The fitted model for % drug release and emulsification time is the quadratic models & expressed as:

TABLE 9: CODED & ACTUAL VALUES

Coded values	Actual values	
	A	B
-1	2	4
0	3.5	5.5
+1	5	6

TABLE 10: 3^2 FULL FACTORIAL DESIGN LAYOUT

Batch no.	Variable level in coded form		% Drug release	Emulsification time (Sec)
	X_1	X_2		
F1	-1	-1	93.43±1.42	62
F2	-1	0	85.35±1.36	66
F3	-1	+1	94.18±1.37	61
F4	0	-1	92.35±2.38	63
F5	0	0	96.37±1.78	56
F6	0	+1	88.29±1.25	63
F7	+1	-1	92.04±1.39	62
F8	+1	0	81.3±2.19	62
F9	+1	+1	87.13±1.54	59

*mean n = 3

Final Equation in terms of Coded & Actual Form of Mirtazapine for % Drug Release: From the ANOVA Values of P less than 0.0500 indicated model terms were significant. In this case, A is not significant and B is significant model terms. It indicates oil percentage having no significant effect on drug release and surfactant/co-surfactant ratio as having significant effect on % drug release. Furthermore, lower difference between predicted & observed result for all batches showed good agreement for the use of quadratic model for optimization.

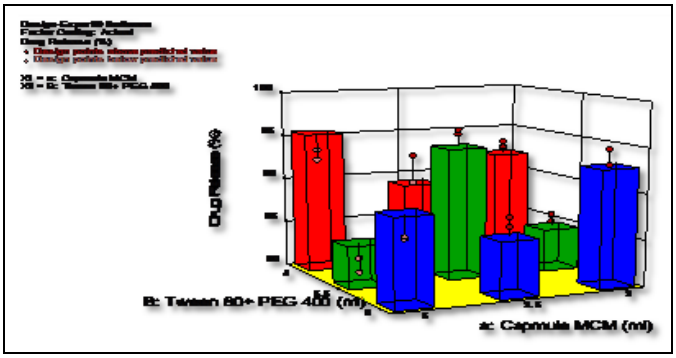

FIG. 10: 3D RESPONSE PLOTS FOR THE EFFECT OF SELECTED VARIABLES ON % DRUG RELEASE OF MIRTAZAPINE

Final Equation in Term of Coded Factor:	Final Equation in Term of Actual Factor:
% Drug Release = 96.36	% Drug Release = 96.36
+2.33* B[1]	+2.33* drug release
-1.93 *B[2]	-1.93 * Oil concentration* Sur-comix
-0.15* a[1] B [1]	-0.15* Oil concentration* drug release
-3.14 *a[2] B [1]	-3.14 * polymer ratio * drug release
-3.24 *a[1] B [2]	-3.24 * Oil concentration* Sur-comix* drug release
+6.54 *a [2] B [2]	+ 6.54 * Oil concentration* Sur-comix

Final Equation in terms of Coded & Actual form of Mirtazapine for Emulsification Time:n From the ANOVA Values of P less than 0.0500 indicated model terms were significant. In this case, A and B are significant model terms. It indicates both oil percentage and surfactant/co-surfactant ratio as having significant effect on emulsification time. Response surface graph indicates that the oil percentage has more significant effect on emulsification time than surfactant/co-surfactant. Furthermore, lower difference between predicted & observed result for all batches showed good agreement for the use of quadratic model for optimization.

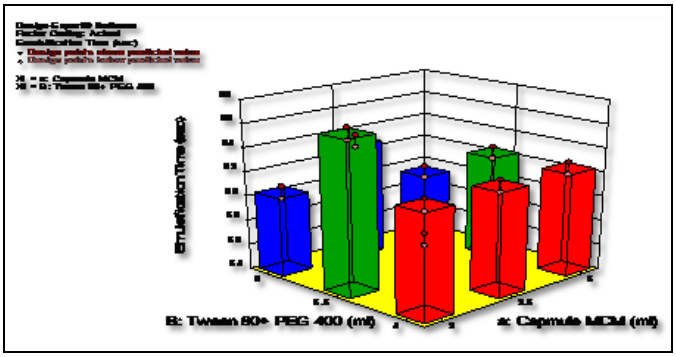

FIG. 11: 3D RESPONSE PLOT FOR THE EFFECT OF SELECTED VARIABLES ON EMULSIFICATION TIME

Final Equation in Term of Coded Factor:	Final Equation in Term of Actual Factor:
Emulsifying Time	Emulsifying Time
61.83	61.83
+ 1.33* A[1]	+ 1.33* Oil concentration
-1.00 *A[2]	-1.00 * Sur-comix
+0.67 *B [1]	+0.67 * drug release
+0.000 *B[2]	+0.000 * Oil concentration* Sur-comix
-1.33 *A[1] B[1]	-1.33 * Oil concentration* drug release
3.33 *A [1]B [2]	3.33 * polymer ratio * drug release
-4.33 *A[2] B[2]	-4.33 * Oil concentration* Sur-comix*drug release

Preparation of Solid SEDDS: Solid SEDDS were prepared from liquid SEDDS by adsorption method.

Evaluation of Prepared Solid SEDDS:

Micromeritic Characterization of Solid Self Emulsifying Drug Delivery System:

TABLE 11: EVALUATION OF PREPARED SOLID SEDDS

Batches	Bulk Density* (g/ml)	Tapped Density* (g/ml)	Carr's Index*	Hausner's Ratio*	Angle of Repose* (θ)
F1	0.7223±0.005	0.7435±0.023	6.85±0.021	1.045±0.39	19.5±0.67
F3	0.8928±0.056	0.8963±0.034	5.78±0.051	1.056±0.004	18.5±0.23
F5	0.7466±0.023	0.7924±0.067	6.84±0.023	1.078±0.02	16.1±0.28
F8	0.7104±0.087	0.7349±0.012	5.14±0.56	1.034±0.53	19.6±0.45

Emulsification Time, Phase Separation & % Drug Content of Solid SEDDS:

TABLE 12: EMULSIFICATION TIME, PHASE SEPARATION & % DRUG CONTENT OF SOLID SEDDS

Formulation code	Emulsification Time in sec	Phase separation	Drug content (%)	Dispersability
F_1	65	No	86.04±0.33	A
F_3	60	No	92.22±0.13	A
F_5	56	No	96.12±2.28	A
F_8	75	No	90.04±0.02	A

In-vitro Dissolution Studies in 0.1 N HCl:

TABLE 13: *IN-VITRO* DISSOLUTION OF SOLID-SEDDS STUDIESIN 0.1 N HCl

Time min	F1	F3	F5	F8
10	40.23±1.78	41.16±2.36	44.86±1.51	42.57±1.52
20	53.87±1.89	52.36±1.39	58.54±1.62	54.28±1.35
30	64.15±2.78	68.79±1.71	72.97±1.38	69.58±1.51
40	74.87±1.98	79.51±1.49	84.58±2.16	80.18±1.62
50	88.13±1.24	89.22±1.37	92.61±1.78	87.63±1.81
60	93.54±1.67	93.86±0.58	96.97±1.89	94.62±1.61

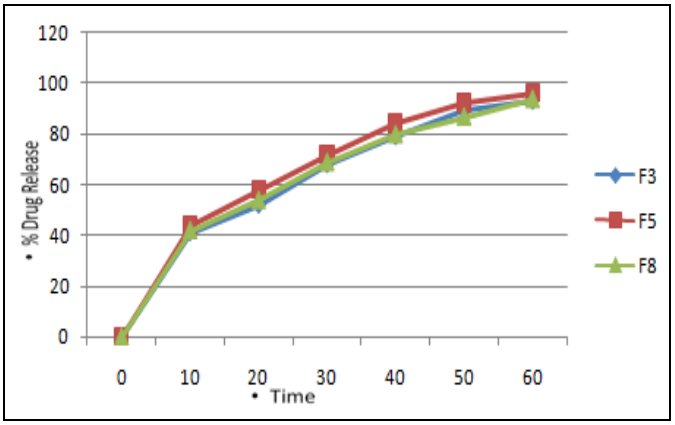

FIG. 12: *IN-VITRO* DISSOLUTION OF S-SEDDS STUDIES IN 0.1 N HCl

Solid-State Characterization of Solid SEDDS:

UV Scans Analysis: The compatibility studies were carried out on the UV spectrophotometer at initial, 2 weeks, 4 weeks. The scanning values were found in the range of 273 to 277 nm maxima and the peaks were also obtained in the range 284-286 nm as minima.

The placebo microemulsion does not contain any of the above peaks. There is no significant variation in the λ_{max} of the prepared microemulsion as compared to the pure drug, which indicates there is no and drug excipient interaction.

TABLE 14: COMPATIBILITY STUDIES OF THE DRUG AND THE EXCIPIENT WITH SOLID CARRIER

S. no.	Drug + Excipient	Initial		II weeks		IV weeks	
		λmax in (nm)					
		Maxima	Minima	Maxima	Minima	Maxima	Minima
1	Mirtazapine+oleicacid+NeusilinUS2	312	318	314	319	312	315
2	Mirtazapine+Tween80+NeusilinUS2	314	319	312	317	312	318
3	Mirtazapine+PEG400+Neusilin US2	313	315	312	319	315	321

DSC Study: DSC of pure Mirtazapine and solid SEDDS are shown in Figure. Pure Mirtazapine showed a sharp endothermic peak at about 114.94 ºC due to crystalline state (A). There was no peak of Mirtazapine found in the solid SEDDS, a sharp endothermic peak was observed at 221.38 ºC of Neusilin indicating that as the drug was dissolved into oil and surfactant mixture then the liquid SEDDS adsorbed onto solid carrier drug must be present in the molecularly dissolved state. As the drug is present in molecularly dissolved state when solid SEDDS diluted with water the adsorbed liquid SEDDS form fine oil droplets containing drug in dissolved state. This dissolved state drug is directly available for absorption and fine size of droplets results in increased effective surface area for absorption overall effect of this is improved bioavailability.

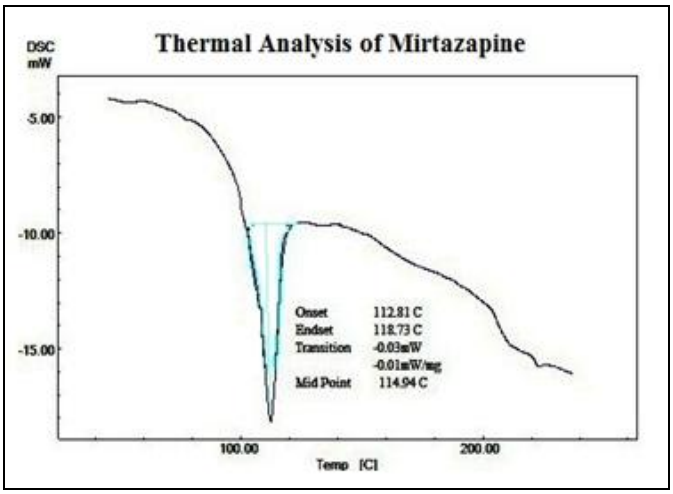

FIG. 13: DSC GRAPH OF MIRTAZAPINE

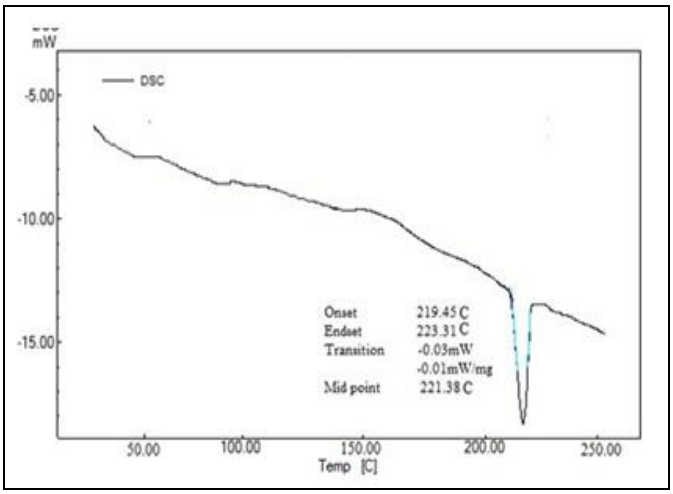

FIG. 14: DSC GRAPH OF FORMULATION

XRD Study: X-ray powder diffractogram for pure drug and solid SMEDDS are shown in Figure. The pure Mirtazapine showed a sharp peak that indicates the drug is in crystalline state. The Mirtazapine in the solid SEDDS showed no sharp peaks indicating that Mirtazapine was solubilized in oil, surfactant mixture and after adsorption on to solid carrier Mirtazapine is present in molecularly dissolved state on to solid carrier.

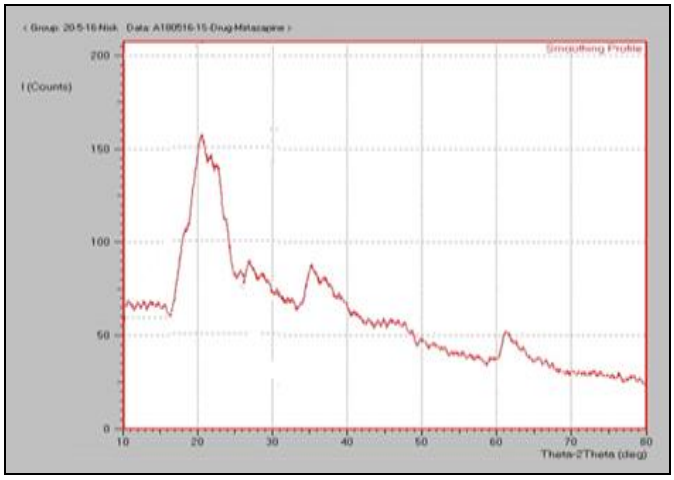

FIG. 15: XRD OF PURE DRUG

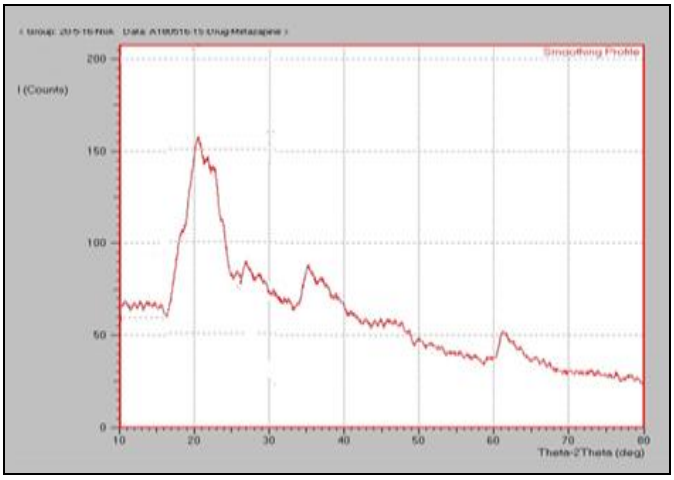

FIG. 16: XRD OF FORMULATION

The SEM image of Neusilin US2 and solid SMEDDS are shown in **Fig. 17** and **18**. NeusilinUS2 appeared as porous in nature and for the solid SMEDDS, it can be clearly seen that the liquid SMEDDS is adsorbed on the surface of Neusilin US2.

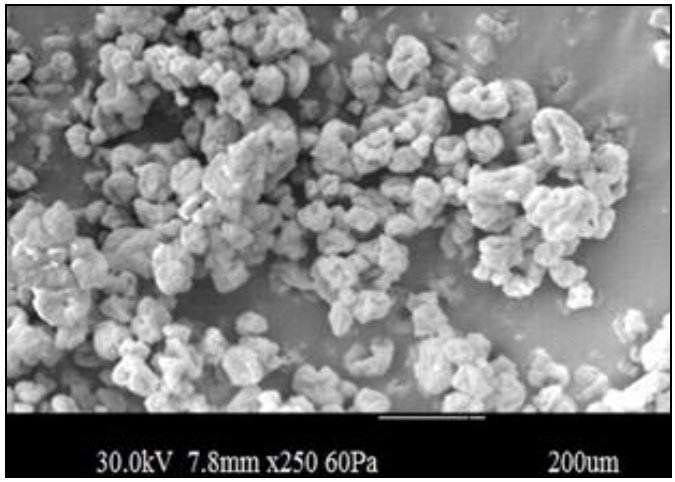

FIG. 17: SEM OF SOLID CARRIER (NEUSILIN)

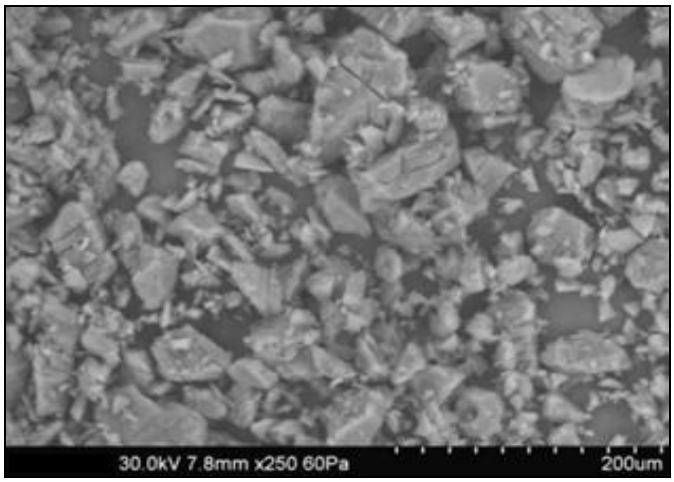

FIG. 18: SEM OF FORMULATION

Zeta Potential:

TABLE 15: RESULT OF ZETA POTENTIAL OF s-SEDDS

S. no.	Batch	Zeta potential
1	F5	-30mv

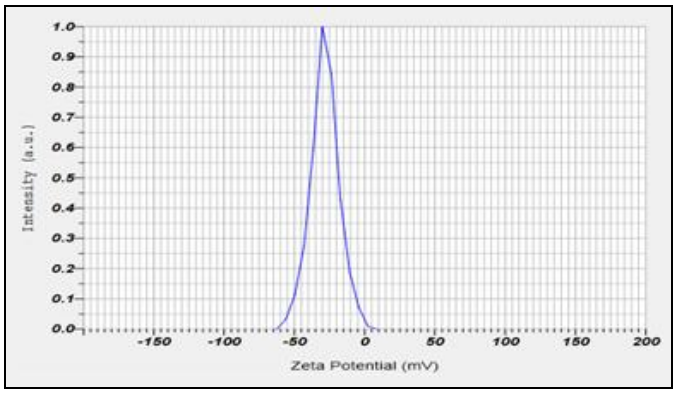

FIG. 19: ZETA POTENTIAL OF OPTIMISED SOLID-SEDD

From the obtained results it was found that F5 showed zeta potential which was much superior as compared to the other batches.

Comparison of *in-vitro* Drug Release of Optimized Batch with Pure Drug: Dissolution profile of prepared solid SEDDS was compared with pure drug. From observation table it was observed that pure drug showed poor dissolution as compared to all three solid SEDDS formulations.

TABLE 16: COMPARISON OF DRUG RELEASE OF OPTIMIZED BATCH WITH PURE DRUG

Time Min	F5	Pure Drug
10	44.86±1.51	20.79±1.99
20	58.54±1.62	27.99±2.05
30	72.97±1.38	32±1.76
40	84.58±2.16	41.48±1.77
50	92.61±1.78	44.3±1.74
60	96.97±1.89	46.7±1.85

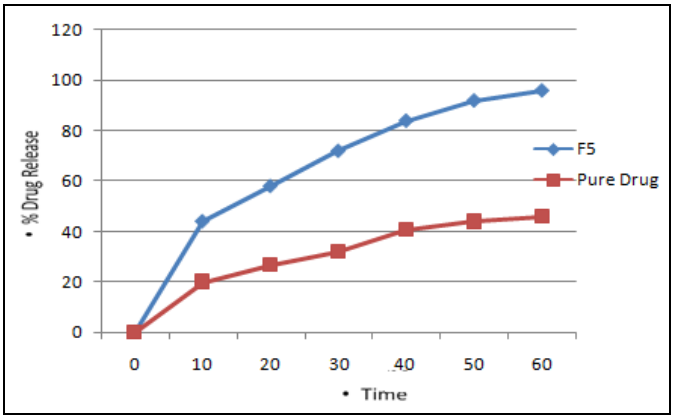

FIG. 20: COMPARISON OF DRUG RELEASE OF OPTIMIZED BATCH WITH PURE DRUG

Stability Study of Solid SEDDS: Solid SEDDS on dilution showed no precipitation of drug. The stability data is shown in **Table 17,** which indicates solid SEDDS of Mirtazapine was physically and chemically stable. Results showed that there was no significant drug loss during the stability test periods.

TABLE 17: STUDY OF SOLID SEDDS

S. no.	Evaluation parameter	Batch F540 ± 2 °C/ 75 ± 5% RH
1	Appearance	No change
2	Drug content of	97.7
3	% drug release	98.67

TABLE 18: *IN-VITRO* DRUG DISSOLUTION AFTER 1 MONTH

Time (min)	Initial % drug release of F5 batch	% drug release F5 after 1 month
10	44.86±1.51	43.25±1.31
20	58.54±1.62	57.34±2.62
30	72.97±1.38	71.77±1.28
40	84.58±2.16	83.58±2.65
50	92.61±1.78	91.71±2.58
60	96.97±1.89	95.86±2.65

CONCLUSION: From the entire study it was concluded that there was an increase in the solubility and dissolution rate of Mirtazapine in S-SEDDS as compared to the dissolution rate of pure Mirtazapine. It was found that there was a dramatic increase in the drug release profile from the formulation. DSC study showed no change in the crystallization temperature and melting point of Mirtazapine. XRD showed the conversion of drug from crystalline form to amorphous form. The release from F_5 SEDDS was increased due to presence of drugs in dissolved state.

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CONFLICTS OF INTEREST: Nil

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