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FORMULATION AND EVALUATION OF SOLID SELF EMULSIFYING DRUG DELIVERY SYTEM OF RANOLAZINE

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ABSTRACT

The Objective of present study was to develop a solid self-emulsifying drug delivery system (SEDDS) of ranolazine to enhance its oral bioavailability. Ranolazine is an anti anginal drug used in the treatment of cardiovascular diseases like chronic angina, ischemia. Solubility of ranolazine in various oils was determined to optimize the oil phase of a SEDDS. Various surfactants and co-surfactants were screened for their ability to emulsify the selected oil. Pseudo ternary phase diagrams were constructed to identify the self emulsification region. Liquid SEDDS were prepared using Oleic acid, Cremophor EL and Transcutol P as oil, surfactant and co-surfactant respectively. Solid SEDDS were prepared using Aerosil 200 as an adsorbent. Solid systems were preferred to SEDDS as they are stable, easy to handle and have improved patient compliance. Prepared Solid systems were evaluated for flow properties, drug content and *in-vitro* drug release. Results showed that prepared Solid systems have good flow property with 97.33% drug content. Dilution study by visual observation showed that there was spontaneous micro emulsification and no sign of phase separation. SEM photograph showed smooth surface of Solid system with no aggregation. Drug release from Solid systems was found to be significantly higher compared to conventional solid dosage form. From the present study it is clear that SEDDS can be formulated to improve the dissolution and oral bioavailability of poorly water soluble drug, ranolazine.

Keywords: Ranolazine, Solid self-emulsifying drug delivery system, Oleic acid, Transcutol P, Cremophor EL, Aerosil200.

INTRODUCTION

The improvement of bio-availability of drugs presents one of the greatest challenges in drug formulations. Various techniques have been utilized to increase drug solubility and dissolution of poorly water soluble drugs exhibiting dissolution rate limited absorption. Among these, self-emulsifying formulations are one of the options to improve the bioavailability of poorly soluble drugs. SEDDS are thermodynamically stable, high solubilization capacity, improvement in bioavailability. These are isotropic mixtures of oil, surfactant, and co-surfactant. These formulations when diluted in aqueous medium with gentle agitation disperse spontaneously to form fine oil in water emulsion. The rate and extent of absorption of poorly water soluble drug incorporated in self-emulsifying formulations increases due to the presence of drug in soluble form in the gastro intestinal tract offering a large surface area for absorption [1].

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The oral bioavailability augmentation is achieved by enhanced dissolution and solubilization of the administered drug by stimulation of biliary and pancreatic secretions, prolongation of gastric residence time [2]. Many techniques are offered to convert conventional liquid SEDDS to solid such as adsorption to solid carriers, spray drying, spray cooling, melt extrusion, supercritical fluid based methods, etc. But among these, the adsorption technique is simple and just involves addition of liquid formulation onto carriers by mixing in a blender. The resulting powder may then be filled directly into capsules or, alternatively, mixed with excipients before compression into tablets. A significant benefit of the adsorption technique is good content uniformity [3].

Ranolazine, an anti anginal drug, used in the treatment of various cardiovascular diseases, belongs to class II in biochemical classification system i.e. low solubility and high permeability. One of the major problems with this drug is its low solubility in biological fluids, which results in poor oral bioavailability. Poor solubility of ranolazine leads to poor dissolution and hence variation in bioavailability. Thus increasing the aqueous solubility and dissolution of ranolazine is of therapeutic importance. Aqueous solubility and dissolution of ranolazine can be increased by formulating in SEDDS. Hence main objective of the study was to develop and evaluate an optimal S-SEDDS formulation of the drug.

MATERIALS AND METHODS

Drug and Chemicals

Ranolazine was generous gift sample from Gattefosse (Mumbai). Cremophor EL (Polyoxyl 35 castor oil) was obtained as gift sample from Croda chemicals (Mumbai) andTranscutol P was obtained from Ayra labs (Hyderabad). Other chemicals Span20 (sorbitan mono laurate), Span80 (sorbitan mono oleate), Tween20 (Polyoxyethylene sorbitanmono laurate), Tween80 (Polyoxyethylene sorbitan mono laurate), Polyethyleneglycol 400 (PEG 400), Polyethyleneglycol 600 (PEG 600) were bought from S.D. Fine Chem (Mumbai).

Selection of self emulsified drug delivery system components Based on solubility studies)[4]

Oils, Surfactants and Co-surfactants

Solubility of ranolazine in various oils, surfactants, and co-surfactants was measured using shake flask method. Solubility studies can be performed by adding an excess amount of ranolazine into each excipient (2ml) followed by sealing in vials. Sealed vials were kept on Rota shaker for 72 hrs for attaining equilibrium. Each vial was centrifuged at 15000 rpm for 10minutes using a centrifuge (REMI, Mumbai) followed by the removal of undissolved ranolazine by filtering with a membrane filter (0.45µm). Samples were suitably diluted with methanol and drug concentration was measured at 272 nm by a UV visible double beam spectrophotometer, using methanol as a blank.

Based on emulsification studies [5]

Surfactant (emulsification study) [5]

Different surfactants (Cremophor-EL, Span20, Span80, Tween20, and Tween80) were screened for the emulsification ability of selected oil phase. Surfactant selection was done on the basis of percentage transparency and ease of emulsification. Briefly, 300mg of the surfactants were added to 300mg of oily phase. The mixture was gently heated at 50^0C for the homogenization of the components. Each mixture, 50mg, was then diluted with distilled water to 50ml in a stoppered conical flask. Ease of emulsification was judged by the number of flask inversions required to yield a homogenous emulsion. Emulsions were allowed to stand for 2hrs and their percentage transmittance was checked at 560nm by a double- beam UV spectrophotometer using distilled water as a blank.

Co-surfactant (emulsification study) [5]

Co-surfactants like Transcutol P and Capmul MCM were screened for SEDDS formulation. Screening of the co-surfactant was conducted on the basis of percentage transmittance and ease of emulsification. 100mg of the co-surfactant and 300mg of selected oil was prepared and evaluated for ease of emulsification and their percentage transmittance.

Construction of Pseudo ternary phase diagram [6]

On the basis of solubility and emulsification study Oleic acid, Cremophor-EL and Transcutol P were selected as oil, surfactant and co-surfactant respectively. To determine the concentration of components for the existing range of SEDDS, pseudo ternary phase diagram was constructed using water titration method at ambient temperature (25°C). The surfactant and co-surfactant were mixed in different volume ratios (1:1, 1:2, 1:3, 1:4, 4:1, 3:1 and 2:1). Oil and surfactant/co-surfactant mixture were mixed thoroughly in different volume ratios(1:9, 2:8, 3:7, 4:6, 5:5, 6:4, 7:3, 8:2 and 9:1w/w) and titrated with water by dropwise addition under gentle agitation. The ratio of one excipient to another in the SEDDS formulation was analyzed and the pseudo ternary plot was constructed using TRIPLOT V14 (4.1.0.2) software.

FORMULATION

Preparation of SEDDS [7]

A series of SEDDS formulations for ranolazine were prepared based on solubility studies, pseudo ternary phase diagram and visual observation. In this study Oleicacid was used as oil, Span80, Cremophor-EL was used as surfactants and Trancutol P, Capmul-MCM were used as co-surfactant respectively. In brief, oil was added to previously weighed ranolazine (unit dose 250mg). The components were then kept in a sonicator at 37°C until drug completely dissolved in oil phase. Surfactant and co-surfactant were then added to the prepared composition and were magnetically stirred until clear emulsion was formed. The formulations were represented in Table 8.

CHARACTERIZATION AND EVALUATION OF SEDDS

Self-Emulsification Time and Dispersibility test[8]

Self-emulsification efficiency of formulation was assessed using a standard dissolution apparatus Type-II, One ml of each formulation was added to 500mL of distilled water at 37 ± 0.5°C. A standard stainless steel paddle rotating at 50rpm provided gentle agitation. The *in-vitro* performance of the formulations was visually assessed using the following grading system as shown in Table 1.

Droplet size and zeta potential determination [9]

A total of 50mg of the optimized SEDDS formulation was diluted with water to 100 ml in a flask, and gently mixed by hand. The droplet size distribution and zeta potential of the resultant emulsion was determined by Malvern Zetasizer (Malvern 2000).

Effect of dilution [10]

The dilution study was done to assess the effect of dilution on SEDDS pre-concentrate. These formulations were subjected to various dilutions (1:50, 1:100, and 1:500) with various diluents (water, 0.1N HCL, pH 6.8 phosphate buffer). Those formulations which did not show any phase separations were considered for further study.

Thermodynamic Stability Studies [11]

To overcome the problem regarding the thermodynamic stability, the following stability studies were performed, which are as follows

a) Heating Cooling Cycle

Heating and cooling cycle was done in refrigerator, the temperature ranging between 4°C and 45°C for 48 hours. The formulations which were stable at these temperatures were subjected to centrifugation test.

b) Centrifugation

Centrifugation study for the selected formulations was done at 3500 rpm for 30 mins using a centrifuge (REMI). Formulations which did not show any phase separation were taken for the freeze thaw stress test.

c) Freeze Thaw Cycle

Three freeze thaw cycles were carried out between a temperature - 4°C and +40°C, where the formulation was stored for not less than 48 hours at each temperature. Those formulations, which passed these thermodynamic stress tests, were selected for further study.

Viscosity determination [12]

Brookfield DVE viscometer (Brookfield Engineering Laboratories, Inc., Middleboro, MA) was used for the determination of viscosity of the formulations. About 0.5 g of sample was taken for analysis without dilution and the viscosity was determined using spindle no. S-34 at 100 rpm at 25±0.5°C.

% Transmittance [13]

1ml of Liquid SEDDS was diluted to 100 ml distilled water and observed for percentage transmittance at 560 nm using UV–visible spectrophotometer against distilled water as a blank.

Preparation of Solid SEDDS (S-SEDDS)[14]

S-SEDDS were prepared by adsorbing liquid SEDDS containing ranolazine on to the Aerosil 200. In brief liquid SEDDS was added drop wise into a porcelain dish containing 1.5 gm of Aerosil 200. After each addition, mixture was homogenized using glass rod to ensure uniform distribution of formulation. Resultant wet mass was passed through sieve no. 120 and dried at ambient temperature and filled into hard gelatin capsule of zero size and stored until further use. The formulations were represented in Table 9.

CHARACTERIZATION OF SOLID SEDDS

Drug Excipient Compatibility Studies

FT-IR offers the possibility of chemical identification, provides information about the structure of molecule. The infrared analysis was carried out to find out the presence of drug-excipient interactions used in the preparation of Solid SEDDS. IR spectra were studied for the pure drug and the optimized formulation was studied in the range from 400-4000 cm^{-1} and carbon black reference.

Angle of Repose

The angle of repose has been used to characterize the flow properties of solids. The flow properties and their corresponding angle of repose are shown in Table 2. Angle of repose is a characteristic related to inter particulate friction or resistance to movement between particles. It is the maximum angle possible between surface of pile of powder or granules and the horizontal plane.

$\tan \theta = h / r$

Where, θ = angle of repose, h = height, r = radius.

A funnel was fixed at a height approximately of 2-4 cm over the platform. The loose powder was slowly passed along the wall of funnel, till the cone of the powder formed. Determine the angle of repose by measuring the height of the cone of powder and radius of the heap of powder [1]. Flow properties and angle of repose were represented in Table 2.

In vitro Dissolution Technique [15]

In vitro dissolution studies were carried out to assess drug release from oil phase into aqueous phase by USP type I dissolution apparatus using 900 ml of 0.1N HCL for 2 hrs and 6.8 pH phosphate buffer for 6 hrs at 100 rpm and temperature was maintained at 37 ± 0.5°C. 5ml of samples were withdrawn at specific intervals of time and volume withdrawn was replaced with fresh medium to maintain sink condition. Samples taken were then analyzed at 272 nm using UV spectrophotometer.

Drug Incorporation Efficiency [16]

Ranolazine content in S-SEDDS was estimated using the UV method. S-SEDDS formulation was dissolved in sufficient quantity of methanol, sonicated for 10mins and filtered. The absorbance of filtrate was checked at 272 nm on UV- Visible Spectrophotometer.

Scanning electron microscopy (SEM) of S-SEDDS

Surface topography of the S-SEDDS was investigated by SEM.

RESULTS AND DISSCUSION

The main objective of the study is to develop Solid self emulsifying drug delivery system of ranolazine using various concentrations of oil (oleic acid) surfactant (Cremophor-EL, Span80) and co-surfactant (Trancutol P, Capmul-MCM).

FTIR studies

FT-IR analysis of optimized formulation and the drug were studied for the interaction of the excipient and the drug in the final formulation. Ranolazine has characteristic absorption peaks **N-H** at 3450.77cm^{-1}, **O-H** at 3570.36 cm^{-1}, **C=O** at 1753.35 cm^{-1}, **C=C** at 1593.6 cm^{-1} and **C-H** at 3039.91cm^{-1} . Similar peaks were observed in spectra of different combinations of excipients and in optimized formulation (Solid SEDDS), along with absence of interfering peaks indicating there is no unwanted reaction between ranolazine and other excipients used in the study. From the Figures1,2 and Tables 6,7 it can be inferred that there was no appearance or disappearance of any characteristic peaks. This shows that there was no interaction between the drug and excipients used in Solid SEDDS preparation.

Screening of Oils/Vehicles, Surfactants and Co-Surfactants

Solubility studies (Screening of Oils/Vehicles, Surfactants and Co-surfactants)

Solubility studies were aimed at identifying a suitable oil phase, surfactants and co-surfactants for the development of the ranolazine SEDDS. The solubility of ranolazine in various oils, surfactants, co-surfactants is presented in Table 3. Oleic acid was selected as an ideal vehicle, Cremophor-EL, Span80 were selected as surfactants, Trancutol P, Capmul-MCM was selected as Co-surfactants, due to high solubility of drug in this excipients.

Based on ease of emulsification:

Screening of surfactants

Surfactants were screened and the results were presented in Table 4. Oleic acid exhibited highest emulsification efficiency with Cremophor-EL (%Transmittance 94.18, No. of flask inversion was 11) and Span 80 (%Transmittance 85.44, No. of flask inversion 18). Based on the emulsification studies Cremophor-EL and Span 80 were selected as Surfactants.

Screening of Co- surfactants

Co-surfactants screening was performed and data is represented in Table 5. Transcutol P and Capmul MCM were selected as Co-surfactants as they exhibit high percentage transmittance with Cremophor EL and Span 80 with less number of flask inversions**.**

Pseudoternary phase diagram

Pseudoternary phase diagrams were constructed to determine self micro emulsifying region and to select suitable concentration of oil, surfactant and co-surfactants .Self micro emulsion region was found to be more for formulation F7S (2:1) and were represented in Figure 3 (b). Which is constructed using Oleic acid as Oil , Span 80 as Surfactant , Transcutol P as Co-surfactant.

Assessment of Self emulsification

The results for self emulsification studies were represented in Table 10.

Viscosities

The viscosities of the various formulations were determined using spindle no.S-34. Viscosities of various formulations are represented in the Table 10.

Stability studies

Thermodynamic stability studies showed that all the formulations were stable with no phase separation. The results were represented in Table 10.

Percent transmittance

Percentage transmittance of various formulations shown in Table 10. Formulation F7 (2:1) was found to be (95.88%), which indicates that the formulation was more transparent compared to other formulations.

Effect of dilution

Formulations was subjected to various dilutions (1:50, 1:100, and 1:500) with various diluents (water, 0.1N HCL, pH 6.8 phosphate buffer). Formulations does not shown any phase separations and results were represented in Table 10.

Zeta potential

Zeta potential and polydispersity index of the resultant emulsion was determined by Malvern Zeta sizer. Zeta potential of optimized formulation was found to be -3.10, polydispersity index is 0.452 and its particle size was 295.5nm. Negative charge on the particles indicates that there is no flocculation, hence the formulation was found to be stable and were represented in Figure 7 and 8.

Characterization of Solid SEDDS

Drug content

Drug content of various formulation are represented in the Table 11. Formulation F7S (2:1) shows 97.33%.

Flow properties

Flow properties for various formulations were performed and represented in Table 11.

***In vitro* dissolution studies**

In-vitro dissolution studies were carried out using type-II dissolution apparatus (Basket type) for all the formulations and formulation F7S (2:1) was optimized as it exhibits high % of cumulative drug release and were represented in Figure 4 and 5 . Then the test formulation was compared with marketed formulation, % cumulative drug release was found to be more for F7S (2:1) formulation compared to marketed formulation. Formulation F7S (2:1) shows drug release (86.961%) where as marketed formulation shows (79.892%). The results of compared *in-vitro* dissolution studies were represented in Figure 6.

SEM

The drug-surfactant concentration is discretely embedded in the oil matrix. The particles were in high abundance, smaller and nearly spherical with size ranging from 100 to 300 nm. The surface of the particles was found to be smooth and porous as shown in Figure 9

CONCLUSION

In the present study, Solid SEDDS of ranolazine were prepared and evaluated for various physicochemical parameters. The optimized formulation F7S (2:1) showed a significant increase in the drug release compared to the conventional solid dosage form. Thus, SEDDS can be regarded as novel and commercially feasible alternative to current ranolazine formulations. Hence it can be concluded that S-SEDDS are promising approach for oral delivery of poorly water soluble compounds.

Table 1: Grades of Dispersibility test

S. No.	OBSERVATION	GRADES
1	Rapidly forming (within 1 min) nanoemulsion, having a clear or slight bluish	A
2	Rapidly forming, slightly less clear emulsion, in bluish colour	B
3	Fines milky emulsion that formed within 2 min.	C
4	Dull, greyish white emulsion having slightly oily appearance that is slow to emulsify (longer than 2 min).	D
5	Formulation, exhibiting either poor or minimal emulsification with large oil globules present on the surface.	E

Table 2: Flow Properties and Corresponding Angles of Repose

Flow Property	Angle of Repose (degrees)
Excellent	25–30
Good	31–35
Fair - aid not needed	36–40
Passable - may hang up	41–45
Poor - must agitate, vibrate	46–55
Very poor	56–65
Very, very poor	>66

Table 3: Screening of Oils/Vehicles, Surfactants, Co-surfactants based on solubility studies

Type of Oil	Solubility (mg/ml)	Type of Surfactant	Solubility (mg/ml)	Type of Co-surfactant	Solubility (mg/ml)
Oleic acid	**79.07**	Cremophor EL	**81.46**	TransutolP	**108.08**
Linseed oil	46.22	Span80	**35.53**	Capmul MCM	**78.65**
Caproyl 90	13.82	Labrasol	12.74	Ethanol	123.25
Castor oil	24.97	Span20	19.57	Glycerol	0.824
Isopropoylmyristate	11.59	Tween 20	14.95	Propylene glycol	5.067
Olive oil	4.88	Tween 80	21.43	Plurololeique	23.63
Labrafil 1944cs	15.37	Etocas	1.12	PEG 400	18.04
Labrafac	9.54	Cremophor RH-40	21.66	PEG 600	29.78
Sunflower oil	3.67			Labrafil M2125	17.08
Soyabean oil	1.32			Isopropyl alcohol	7.02

Table 4: Screening of surfactants based on emulsification

S. No.	Type of surfactant	No. of flask inversion	% transmittance at 560nm
1	Cremophor -EL	11	94.18
2	Cremophor RH-40	65	45.08
3	Span 80	18	85.44
4	Span20	32	65.31
5	Tween20	26	32.09
6	Tween80	38	27.23

Table 5: Screening of Co-surfactants based on emulsification

S. No.	Type of Co-surfactant	No. of flask inversion		% transmittance at 560nm	
		Cremophor -EL	Span 80	Cremophor -EL	Span 80
1	PEG 400	17	24	62.45	50.01
2	PEG 600	21	29	58.09	44.89
3	Transcutol P	8	17	97.6	88.03
4	Capmul MCM	13	23	85.22	79.64
5	Labrafil M2125	29	41	52.13	49.07

Table 6: Characteristic IR peaks of pure drug

Functional Group	Observed value(cm^{-1})	Reported value (cm^{-1})
N-H	3500-3300	3450.77
O-H	3570-3450	3570.36
C=O	1760-1680	1753.35
C=C	1650-1450	1593.6
=C-H (Aromatic)	3050-3000	3039.91

Table 7: Characteristic IR peaks of optimized formulation

Functional Group	Observed value(cm^{-1})	Reported value (cm^{-1})
N-H	3500-3300	3439.19
O-H	3750-3450	3439.19
C=O	1760-1680	1753.35
C=C	1650-1450	1597.11
=C-H (Aromatic)	3050-3000	3020.63

Table 8: Formulation of SEDDS

Formulation	Ranolazine (Drug) (mg)	Oleic acid (Oil) (%w/w)	Cremophor –EL (Surfactant) (%w/w)	Transcutol –P (Co-Surfactant) (%w/W)
F1(1:1)	250mg	50	25	25
F2(1:2)	250mg	50	16.6	33.3
F3(1:3)	250mg	50	12.5	37.5
F4(1:4)	250mg	50	10	40
F5(4:1)	250mg	50	40	10
F6(3:1)	250mg	50	37.5	12.5
F7(2:1)	250mg	50	33.3	16.6
		Oleic acid (Oil) (%w/w)	Span 80 (Surfactant) (%w/w)	Capmul-MCM (Co-Surfactant) (%w/W)
F8(1:1)	250mg	50	25	25
F9(1:2)	250mg	50	16.6	33.3
F10(1:3)	250mg	50	12.5	37.5
F11(1:4)	250mg	50	10	40
F12(4:1)	250mg	50	40	10
F13(3:1)	250mg	50	37.5	12.5
F14(2:1)	250mg	50	33.3	16.6

Table 9: Formulation of Solid SEDDS

Formulation	Ranolazine (Drug)	Oleic acid (Oil) (%w/w)	Cremophor –EL (Surfactant) (%w/w)	Transcutol –P (Co-Surfactant) (%w/W)	Aerosil200 (Adsorbent)
F1(1:1)	250mg	50	25	25	1.5gm
F2(1:2)	250mg	50	16.6	33.3	1.5gm
F3(1:3)	250mg	50	12.5	37.5	1.5gm
F4(1:4)	250mg	50	10	40	1.5gm
F5(4:1)	250mg	50	40	10	1.5gm
F6(3:1)	250mg	50	37.5	12.5	1.5gm
F7(2:1)	250mg	50	33.3	16.6	1.5gm
		Oleic acid (Oil) (%w/w)	Span 80 (Surfactant) (%w/w)	Capmul-MCM (Co-Surfactant) (%w/W)	
F8(1:1)	250mg	50	25	25	1.5gm
F9(1:2)	250mg	50	16.6	33.3	1.5gm
F10(1:3)	250mg	50	12.5	37.5	1.5gm
F11(1:4)	250mg	50	10	40	1.5gm
F12(4:1)	250mg	50	40	10	1.5gm
F13(3:1)	250mg	50	37.5	12.5	1.5gm
F14(2:1)	250mg	50	33.3	16.6	1.5gm

Table 10: Evaluation parameters of SEDDS

FORMULATION	Assessment of Self emulsification	Viscosity	Percent transmittance	Effect to dilution	Centrifuga-tion test (phase separation)	Freeze thaw method (-4°C for 2 days and +40°C for 2 days)
F1(1:1)	Grade A	33±4.29	90.67±4.17	Pass	No	No change
F2(1:2)	Grade A	40±5.83	91.23±3.96	Pass	No	No change
F3(1:3)	Grade B	45±4.62	88.18±3.33	Pass	No	No change
F4(1:4)	Grade A	44±5.65	94.59±4.70	Pass	No	No change
F5(4:1)	Grade B	52±3.89	87.31±5.41	Pass	No	No change
F6(3:1)	Grade B	46±3.46	86.84±3.57	Pass	No	No change
F7(2:1)	Grade A	31±2.22	95.88±3.12	Pass	No	No change
F8(1:1)	Grade B	51±5.62	85.43±3.88	Pass	No	No change
F9(1:2)	Grade A	67±3.22	86.11±4.25	Pass	No	No change
F10(1:3)	Grade A	61±2.87	86.29±3.67	Pass	No	No change
F11(1:4)	Grade A	54±4.11	90.64±3.94	Pass	No	No change
F12(4:1)	Grade B	73±3.08	80.16±2.66	Pass	No	No change
F13(3:1)	Grade A	53±4.21	81.44±4.20	Pass	No	No change
F14(2:1)	Grade A	43±5.14	89.53±3.79	Pass	No	No change

Table 11: Evaluation parameters of Solid SEDDS

Formulation	Drug content	Angle of repose
F1S(1:1)	91.55±3.31	29.21±3.11
F2S1:2)	90.21±3.39	33.28±3.46
F3S(1:3)	85.37±2.78	32.54±3.97
F4S(1:4)	88.91±4.22	41.36±4.63
F5S(4:1)	91.44±5.15	38.70±5.43
F6S(3:1)	96.28±2.17	36.98±3.98
F7S(2:1)	97.33±3.69	28.09±2.77
F8S(1:1)	87.36±3.07	32.88±4.88
F9S(1:2)	90.22±2.38	39.67±5.43
F10S(1:3)	89.34±3.22	41.43±4.12
F11S(1:4)	91.15±3.17	41.08±3.09
F12S(4:1)	90.68±4.09	45.32±4.82
F13S(3:1)	96.13±4.27	43.28±2.43
F14S(2:1)	95.24±2.13	33.11±3.17

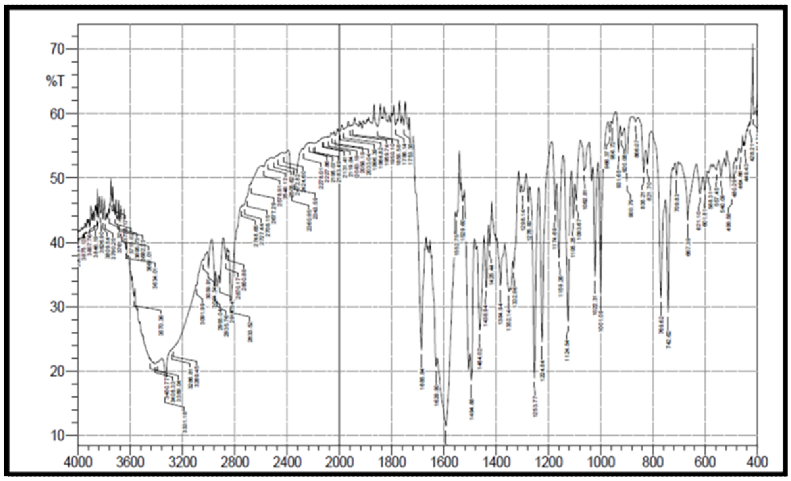


Figure 1: FTIR spectra of pure drug

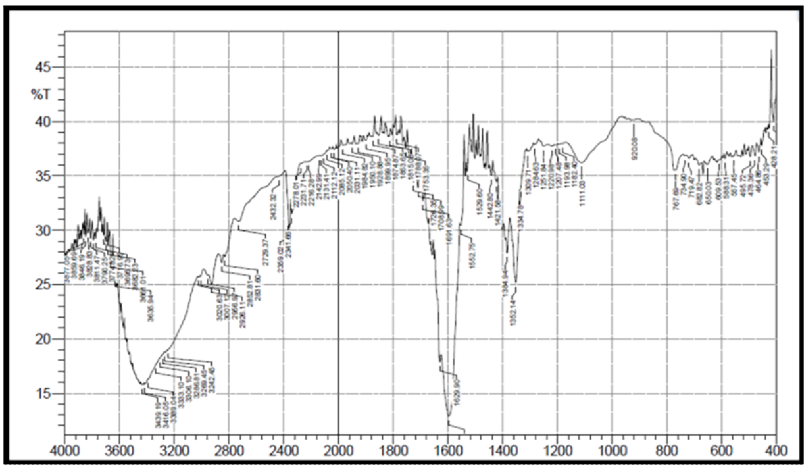
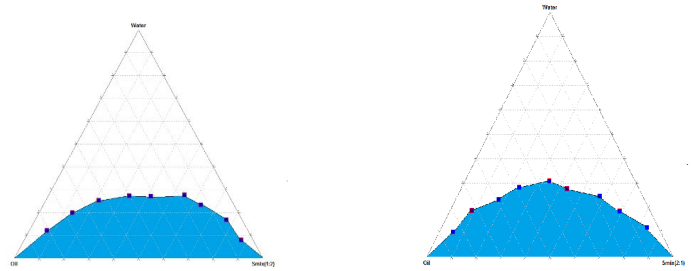


Figure 2: FTIR spectra of formulation

S/CoS ratio is 1:2(38%) **S/CoS ratio is 2:1(39%)**



S/CoS ratio is 1:4(32%) **S/CoS ratio is 4:1(36%)**

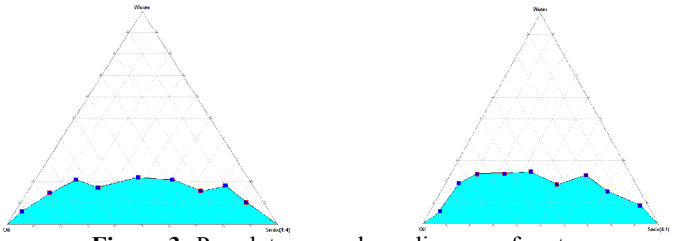


Figure 3: Pseudoternary phase diagram of system

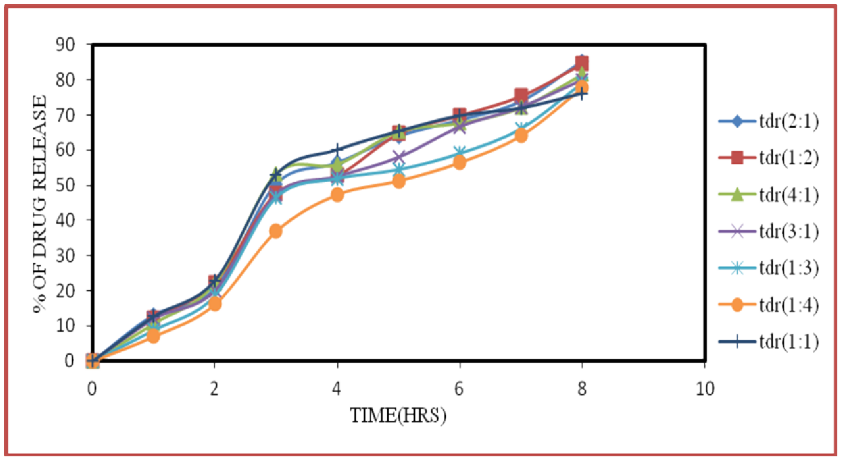


Figure 4: Percent cumulative drug release of Solid SEDDS Formulation (F1-F7)

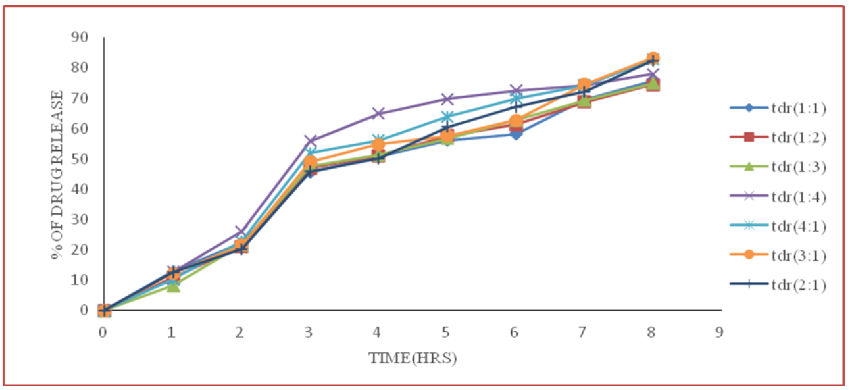


Figure 5: Percent cumulative drug release of Solid SEDDS Formulation (F8-F14)

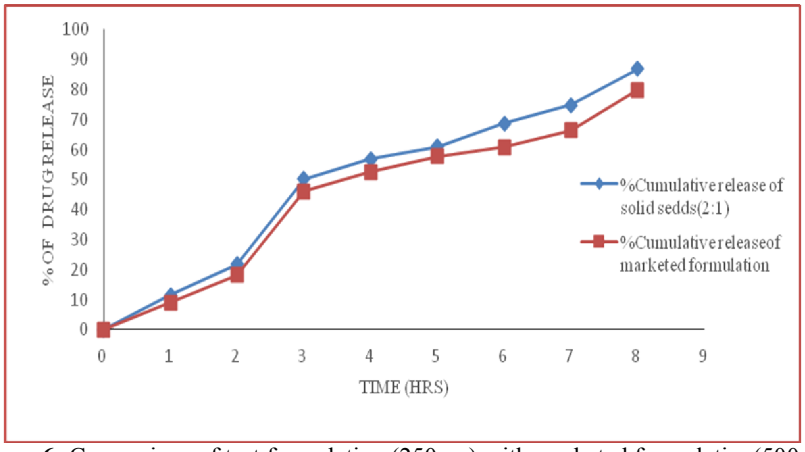


Figure 6: Comparison of test formulation (250mg) with marketed formulation(500mg)

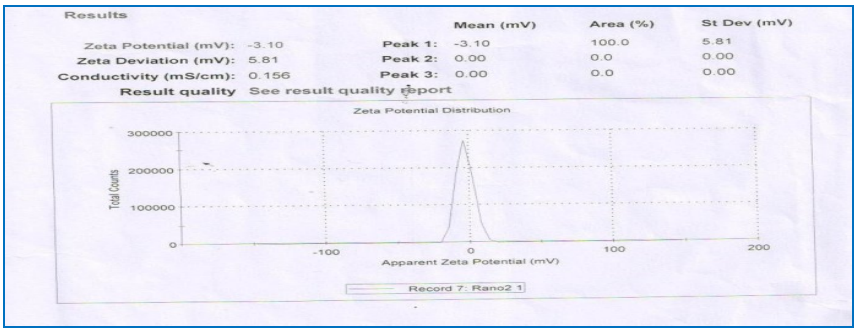


Figure 7: Zeta potential of optimized formulation

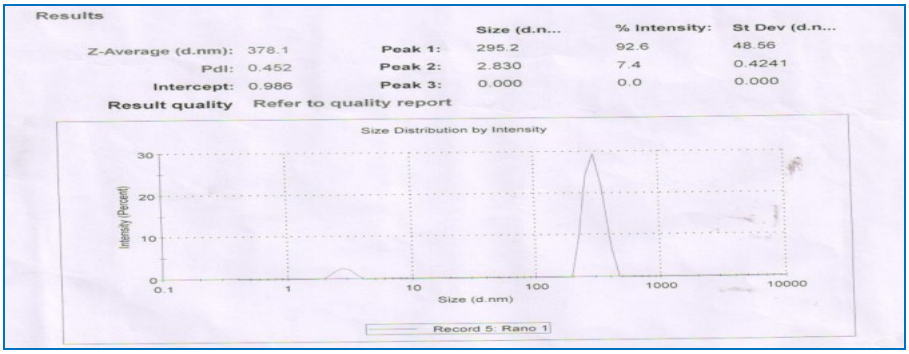


Figure 8: Polydipersity index of optimized formulation

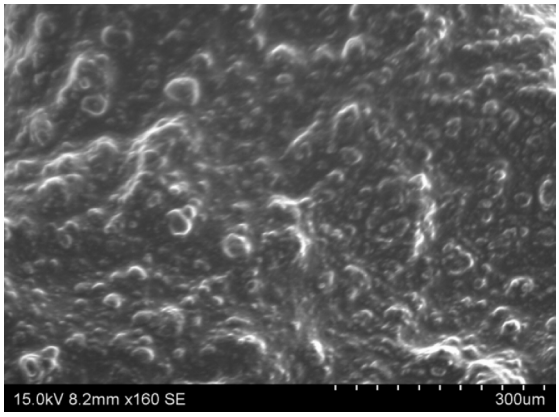


Figure 9: Surface morphology of Solid SEDDS

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