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Research Article

Study of Oral Lipid Based Formulation through Design and Evaluation of Solid Self Emulsified Drug Delivery System

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Abstract

Solid self-emulsifying drug delivery systems (SEDDS) for propylene glycol monoesters (Capmul PG-8NF) were developed using Polaxomers (i.e., Pluronic 127 and Pluronic 68) as both solidifying and emulsifying agents. The present research work aimed at formulation development, and optimization of solid SEDDS using factorial design, and evaluation of solid SEDDS. Different mixtures of solidifying agents were heated to 65^{0}C until homogeneously mixed clear liquids were formed. Solubility of the selected drug Nimorazole was accessed in different oils. Solid SEDDS were then formulated using melt method and solvent evaporation method. Percent transmittance (%T) test study was performed to identify the efficient self-emulsifying formulations. Those formulations which showed higher value for %T were evaluated for droplet size, polydispersity index, ζ potential, refractive index and cloud point measurement. Effect of drug loading on droplet size, increasing dilution in different media, thermodynamic stability and in vitro dissolution was performed to observe the performance of the selected formulation. All of the oils accessed for drug solubility, Capmul PG 8 NF showed higher solubility capacity for Nimorazole. Capmul PG 8 NF was better self emulsified using combination of Pluronic 68 and Pluronic127 surfactant. Droplet size was as low as 65.85µm with polydispersity index and ζ potential 0.418 and -17.12mV respectively. The selected undiluted formulation showed refractive index values ranging from 1.35 to 1.47 indicating the isotropicity of the formulation. The selected formulation was robust to dilution in different media and thermodynamically stable. The maximum % drug release was found to be 99.39±0.6 from the S3 formulation as compare to other formulation. Our study demonstrates a novel approach of developing solid formulation of liquid propylene glycol monoester by incorporating combination of solidifying agents.

1. INTRODUCTION

Poor aqueous solubility and low absorption often hinders the efficacy of lipophilic drug after in vivo administration[1]. Self emulsifying drug delivery systems are isotropic mixtures of oil, surfactant, co-surfactant and drug with a unique ability to form fine oil in water emulsion upon mild agitation following dilution with aqueous phase[2-5]. The present research firstly aims to increase the solubility as well as bioavailability of the Nimorazole (N-2-morpholinoethyl-5-nitroimidazole) BCS class IV drug. It is an antiprotozoal agent to be effective in trichomonal infection and also effective in cancer acts as a radioactive sensitizer[6,7]. The study focuses on the efficacious method of formulating the solid SEDDS by using combination of Pluronic F68 and Pluronic F127 as surfactant and solidifying agent and Capmul PG 8 NF as oil phase, and comparing between melt method and solvent evaporation method to increase the stability of drug as well as to have improved formulation characteristics.

2. MATERIALS AND METHODS

Nimorazole was received as a gift from Lupin research park, Capmul PG 8 NF, Capmul MCM, Captex200, Captex300, Capte x 355 were generous gift from ABITEC corporation. Tween 80 (AR grade), Almond oil and Olive oil was local purchased, Lafrafac cc, Labrasol were received gift sample from Gattefosse.

2.1 Drug Solubility Determination

Solubility studies were conducted by placing an excess amount of Nimorazole (Approximately 300 mg) in a vial containing 2 ml of the oils, and the mixture was mixed manually for ½ hour using a glass rod. After that mixture was placed for sonication for 2hrs. Then mixture was allowed to equilibrate for 48h in a water bath. The equilibrated sample was centrifuged at 3000 rpm for 15 min. The undissolved Nimorazole settle down at the bottom. The supernatant was taken out and diluted with ethanol for quantification of Nimorazole by UV spectrophotometer at λ_{max} 297 nm. The calibration curve was given by the equation:

$$y = 0.008x - 0.002, R^2 = 0.992$$

Where y represents area under the curve and x the concentration in gram per millilitre. The method was validated for accuracy,precision,specificity and solution stability.All meassurements were done in triplicate.

2.2 Experimental Design Optimization of Nimorazole-Loaded SEDDS

Initially the best suitable oil, surfactant and co-surfactant were selected in accordance with studies performed, and taking into account the utility of the experimental design methodology as a very good tool for studying preparation of good emulsions. Formulation composition of prepared SEDDS of Nimorazole is given in Table 1 and 2. Factorial design was constructed to estimate the best amount of Nimorazole in SEDDS, with combinations from two factors (independent variables) which were surfactant: co-surfactant ratio (X1) and concentrations of surfactant mixture(X2).Droplet size (Y1), drug release (Y2) and % transmission (Y3) were dependent variables. The responses of model formulations were treated by Design-Expert® Version 8.0.7.1 software[9].

In the entire formulations drug Nimorazole (300mg) was kept constant. Fifteen formulations were formulated as per experimental design.

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Table 1: Variables in Optimization Study

Variables	Factor
Independent	
X1	Surfactant: co-surfactant Ratio (0.25:0.75;0.5:0.5;0.75:0.25)
X2	Concentration of surfactant mixture (30%- 70%)
Dependent	
Y1	Droplet size (micrometer)
Y2	Drug release (%)
Y3	Transmission (%)

Table 2: composition of self emulsifying drug delivery system (sedds) of nimorazole

Sr. No	Oil (Capmul PG8NF)	F.C	S: Co-s (C) (0.25+0.75)	F.C	S: Co-s (A) (0.5:0.5)	F.C	S: Co-s (B) (0.75:0.25)
1	70%	L1	30%	L6	30%	L11	30%
2	60%	L2	40%	L7	40%	L12	40%
3	50%	L3	50%	L8	50%	L13	50%
4	40%	L4	60%	L9	60%	L14	60%
5	30%	L5	70%	L10	70%	L15	70%

F.C.-Formulation code, S: Co-s (C)-Surfactant to co-surfactant ratio

2.3 Preparation of Self –Emulsifying Formulation with Selected Oil

A series of SEDDS pre-concentrate were prepared compromising Capmul PG 8NF as an oil phase and using combination of Pluronic F 68 with Pluronic F 127.Non-ionic surfactant combination(Smix) were examined at various ratios 0.5:0.5,0.25:0.75,and 0.75:0.25.The samples were prepared using oil and surfactant combinations at ratios 7:3,6:4,1:1,4:6 and 3:7 by two techniques. Firstly, A batch size of 5gms was prepared in which each solidifying agent was weighed according to its ratio in the mixtures and then melted in glass vials on a hot plate until a clear solution was formed. The weighed amounts of lipids were equilibrated at the corresponding temperature and added to the melt. All samples were vortex mixed, in the molten state to ensure homogeneity. secondly, from each ratio of surfactant mixture one combination of oil surfactant ratio was selected (i.e 30%oil concentration), the lipid surfactant mixture and drug was dissolved in ethanol to form clear solution and instead of heating we allowed it to evaporate the alcohol at room temperature and form solid homogeneous solution.

2.4 Characterization and Evaluation of the Selected Formation

2.4.1 % Transmission Study

1mg equivalent of drug mixture were then introduced into a 500ml measuring cylinder containing 100ml of distil water,pre-equilibrated at 30^{0}C.The measuring cylinder was then inverted (rocked) once to provide minimum amount of shear for self-emulsification/dispersion. The transmittance was determined for mixture with drug loading. The resulting emulsions were observed visually for the relative turbidity,appearance and ease of emulsification.The emulsion were allowed to stand for 30 min and their % Transmittance (%T) was measured at 650 nm by UV-1800 double beam spectrophotometer (Shimadzu,Japan formulationn) using double distilled water as blank. Higher value of %T denotes formation of transparent system and thus help in denoting the formed emulsion.So this technique was used instead of pseudoternary phase diagram where visual observation is made and thus are chances of human error.

2.4.2 Determination of Droplet Size and Polydispersity Index

The globule size determination as performed using photon correlation spectroscopy with in-built zetasizer (model: nano zs, malvern instrument, westborough, MA, USA) Aliquot preconcentrate equivalent to 1mg drug was diluted to 50mL with distill water; stirred slowly to form dispersion. Diluted samples were directly placed in to the module for measurements. Measurements are made in triplicate.

2.4.3 In Vitro Dissolution Studies in 0.1N HCL

In vitro dissolution of solid SEDDS formulations was carried out by using dissolution test apparatus USP XXII (paddle type).The solid SEDDS were filled into size '0' capsules batches and kept in the flask of the dissolution apparatus. The dissolution fluid (900 ml) was maintained at 37ºC±0.5ºC. The speed of the stirrer was adjusted at a speed of 50 rpm. An aliquot of 5 ml was withdrawn by means of a pipette at predetermined intervals for a period of 15 minutes. Same quantity of fresh fluid equilibrated at 37ºC±0.5ºC was replaced to maintain apparent sink conditions inside the dissolution compartments. The aliquots were assayed spectrophotometrically at a maximum of 297 nm by using Shimadzu UV-1800 spectrophotometer[8].

2.4.4 Zeta Potential Determination

SEDDS equivalent to 1mg of drug was diluted to 50 mL with distill water in glass beaker with constant stirring. Zeta potential of the resultant emulsion was determined using the zetasizer (model: nano zs, malvern instrument, westborough, MA, USA). Electrophoretic mobility (µm/s) was measured using small volume disposable ζ cell and converted to ζ potential by in-built software using Helmholtz- Smoluchowski equation. All determination were made in triplicate.

2.4.5 Refractive Index Determination

The isotropicity of the SEDDS preconcentrate (undiluted) in molten state was determined by refractive index measurement. Refractive index was measured by Abbe's refractometer.

2.4.6 Cloud Point Measurement

Cloud point temperatures (Tc) were determined by visual observation 0.5 mg equivalent of preconcentrate was diluted to 50mL with distill water in glass beaker. The sample was heated at the rate of 0.5 ^{0}C /min. A close observation was made at the appearance of the dispersion with the increase in temperature. The temperature at which the dispersion become cloudy was taken as Tc. After the temperature exceeds the cloud point, the sample was cooled below Tc, and then it was heated again to check the reproducibility of the measurements.

2.5 Effect of drug loading on droplet size

Effect of drug loading on globule size of emulsion was studied using optimised composition formulation were prepared with and without nimerazole. The resultant SEDDS preconcentrate, 0.5 mg equivalent was diluted to 50 mL with double distill water and the mean globule size of the resulting emulsion was determined by zetasizer (model: nano zs, malvern instrument, westborough, MA, USA).

2.6 Effect of dilution in different media

Dilution study was done to access the effect of dilution on SEDDS preconcentrate, in order to mimic physiological dilution process after oral administration. In this study selected formulation were subjected to increasing dilution (i.e. 10, 100, times) and various diluents i.e. double distilled water, simulated gastric fluid (SGF)

simulated intestinal fluid (SIF). Visual observation were recorded and graded as per grade given below.

- Grade I- Rapid forming emulsion, which is clear.
- Grade II - Rapid forming, slight less clear emulsion, which has a bluish white appearance.
- Grade III - Bright white emulsion (similar to milk like appearance).
- Grade IV - Exhibit poor or minimal emulsification with large oils droplets present on the surface.
- Grade V - Phase separation
- Grade VI - Drug precipitation

2.7 Thermodynamic Stability Study

The objective of thermodynamic stability is to evaluate the phase separation and effect of temperature variation on SEDDS formulation nimorazole SEDDS were diluted with aqueous medium were centrifuged at 15,000 rpm for 15 min and then observed visually for phase separation. Further formulation were subjected to freeze thaw cycles (-20^{0}C for 2 days followed by+40^{0}C for 2 days) and were observed for appearance,phase separation.

2.8 Differential Scanning Calorimetry (DSC)

The thermal characteristics of formulation and drug were determined using Differential scanning calorimeter**.** The samples (about 3.00 mg) were placed in standard aluminum pans, and dry nitrogen was used as effluent gas.

2.9 Powder X-ray Diffractometry

To verify the physical state of Nimorazole in solid SEDDS, X-ray powder scattering measurements were carried out with an X'Pert PRO diffractometer.

2.10 Microscopic Examination

Solid preconcentrates were analyzed using an Motic Digital Biological scope (Lab.Hosp.corporation Mumbai model-223). In Fluorescence microscopy,yellow fluorescence used.Small quantity of molten formulations were placed on a glass slide and covered with glass cover slip,observed under the the scope and captured the images.

3. RESULTS AND DISCUSSION

3.1 Drug Solubility Determination

Solubility of nimorazole in various oils is indicated in Table 3. Caprilic acid content is found to influence the solubility of drug in oils. (C8 content in Capmul PG 8 NF,Capmul MCM, Captex200, Captex300, Captex355, Almond oil, Olive oil are 98,66.8,50-80,55-85,55,0, and 0% repectively; data provided by the manufacturer). Solubility of drug in selected oils was found to be in the decreasing order of Capmul PG 8 NF> Capmul MCM> Captex200> Captex300> Captex355> Almond oil> Olive oil. Based on the maximum solubility Capmul PG 8 NF was selected as oil phase. On mixing the oil with pluronic(melt method) alone it was found that maximum amount of pluronic F68 that can solidify oil phase was 600mg/ml sufficient to make semisolid mass and that with pluronic F127 was 800mg/ml to make semisolid mass but when used in combination 429mg/ml was sufficient to solidify and emulsify and therefore combination of Pluronic F 68, Pluronic F 127 were selected as surfactants and solidifying agents for further study.

Table 3: Solubility of Nimorazole in selected oils

S.No.	Name of Excipient	mg/ml	Use/category
1.	Capmul PG8 NF	198.75	Vehicle
2.	Capmul MCM	171.25	Vehicle
3.	Captex 200	59.75	Vehicle
4.	Captex 300	14.87	Vehicle
5.	Captex 355	11.37	Vehicle
6.	Almond oil	11.25	Vehicle
7.	Olive oil	10	Vehicle

3.2 Preparation of Self-emulsifying Formulation with Selected Oil

Two methods were used for preparation of SEDDS. Observation of melt method indicated that formation of needle crystals of drug on solidification which on vortexing in molten state disappeared. So one formulation from each ratio of surfactant mixture (i.e., three formulations) at 30% oil concentration were selected showing maximum stability % transmittance and minimum droplet size for further study and compared. To improve the stability of the drug in formulation the drug was dissolved in common solvent for drug, oil and surfactants to reformulate the three formulations by solvent method and further characterized as below.

Combinations of nonionic surfactants were studied for their ability to self-emulsify the selected oils. %T versus surfactant concentration were plotted to denote the system which disperse into a emulsion, indicated by the higher value of %T. Higher value of %T denotes that the system has small globule size and thus less scattering. Emulsifying capacity was studied with different ratios of Pluronic F 68 and Pluronic F 127 (0.5:0.5, 0.25:0.75, and 0.75:0.25) by using melt and solvent evaporation method. %T values increased as the ratio increased, indicating the effect of different ratios of surfactants in formation of emulsion. Enhanced capacity was observed for 0.75:0.25 ratio of surfactant in solvent evaporation as compared to melt method. In melt method %T values found low as compared to solvent evaporation, Melt method showed poor emulsifying capacity to the selected oil. It was observed that in solvent evaporation method, the oil tend to be emulsified to the greatest extent than the melt method. Since such oils penetrate to a greater extend into the hydrocarbon chain of the surfactant and itself act as co-surfactant further reducing the interfacial tension and promoting spontaneous emulsification.

3.3 Optimization

The statistically significant relationship between the dependent and independent variables are constructed based on the ANOVA results (Table 4). The effect of surfactant: co- surfactant ratio (X1) and concentration (X2) when droplet size (Y1) is considered as response Fig. 2. Change in the surfactant to co surfactant ratio shows change in the droplet size. Relatively smaller droplet size is obtained with the maximum surfactant to co- surfactant ratio.The highest amount of Nimorazole is released with maximum surfactant: co surfactant ratio and concentration. Increasing the surfactant to co-surfactant concentration shows increase in the % transmission shows the surface response plot for % transmission. From the obtained results it can be concluded that an optimal Nimorazole-loaded SEDDS formulation may be composed of Capmul PG 8 NF, Pluronic F 68, Pluronic F 127 as a surfactant.

Table 4: Summary of results of regression analysis for response

Response	Models	F value	Prob > F	R^2	Adjusted R^2	Predicted R^2	S.D.	Remarks
Y_1(Drug release)	2F1	114.02	0.0001	0.9503	0.9421	0.9195	1.64	Suggested
Y_2(Droplet size)	2F1	49.47	0.0001	0.9311	0.9123	0.8964	0.038	Suggested
Y_3 (% transmission)	2F1	33.94	0.0001	0.9417	0.9217	0.8592	0.45	Suggested

Equation: $Y1=A_0+A_1X_1+A_2X_2+A_3X_3+A_{12}X_1X_2+A_{13}X_1X_3+A_{23}X_2X_3$

(a)Droplet size : $Y1=0.32-0.050X_1-0.16X_2+0.10X_3$ (b)% Drug release: $Y2=78.44+3.75X_1+13.96X_2-1.69X_3$

% Transmission

(c)$Y3=94.83+5.94X_1-0.1173X_2+0.2340X_3-15.52X_1X_2+8.33X1X3$

In transmission study the %T versus surfactant concentration were plotted to denote the system which disperse into a emulsion, Higher value of %T denotes that the system has small globule size and thus less scattering. Emulsifying capacity was studied with different ratios of Pluronic F 68,Pluronic F 127. %T values increased as the ratio of surfactant:co-surfactant increased, indicating the effect of different ratios of surfactants in formation of emulsion. Enhanced capacity was observed for 0.75:0.25 ratio of surfactant as compare to other ratio. 3D surface plot for % transmission shown in Fig.1.

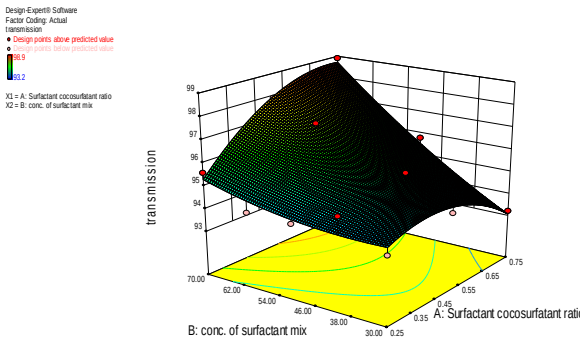

Fig.1: 3D surface plot for % transmission

The particle size distribution is one of the most important characteristics affecting the in vivo fate of emulsions. The globule size of the emulsion also determines the rate and extent of drug release.3D surface plot for droplet size shown in Fig.2. The smaller the globule size, larger the surface area provided for drug absorption. From all the formulation batches , the globule size of resulting emulsion was lowest for formulation S3 The average size of the resultant emulsion after dilution was found to be 65.85µm, These results of decrease in globule size are supported by transmittance evaluation. Interestingly it was found that as the transmittance value increases globule size decreases.

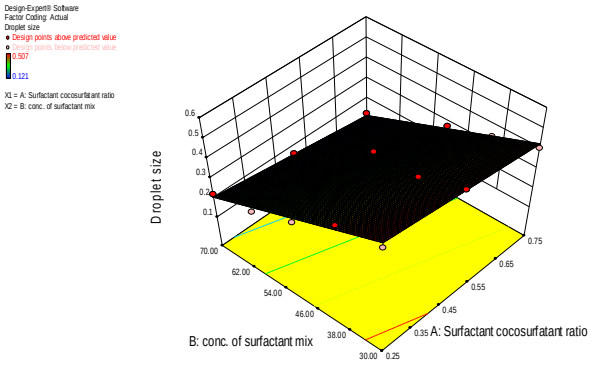

Fig.2. 3D surface plot for droplet size

Dissolution studies were performed for SEDDS containing 300 mg nimorazole.The release of nimorazole from these formulation was evaluated . The S3 Formulation showed rapid release of the drug as compared to the other formulation. Increasing the surfactant to co-surfactant concentration shows increase the drug release mention in Fig.3.

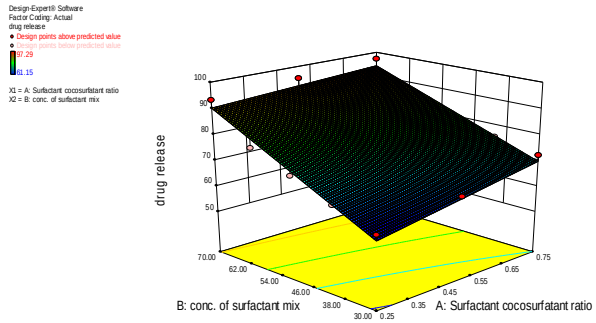

Fig. 1: 3D surface plot for % transmission

3.4 Characterization and Evaluation of the Selected Formation

The selected formulation (with and without drug) were further evaluated for mean particle size, ζ potential, polydispersity index. Drug was loaded at 300 mg per formulation, the result are indicated in the Table 5 and 6.

3.5 Mean Particle Size and Polydispersity Index

Smallest particle size was observed for formulation prepared by solvent evaporation, while largest particle size was observed for formulation prepared by melt method This would be attributed to the emulsifying property of the surfactant with the selected oil. After drug loading there was significant increase in particle size .The particle size observed for all the formulation was less than 101µm. Drug loading didn't showed significant difference in the polydispersity values.

3.6 ζ Potential Determination

The ζ potential values were found to carry negative charges due to the presence of polyoxyethylene copolymer. Significant increase in the value of ζ potential was observed after drug loading. Higher absolute values of ζ potential generally, indicated an increase of electrostatic repulsive forces between emulsion droplets preventing the coalescence droplets and increase in the stability.

3.7 Refractive Index

There was no significant difference in the refractive index values of the formulation tested.The refractive index close to that of water (1.333) prove the isotropicity of the system, the result are indicated in the Table 5 and 6.

3.8 Cloud Point Determination

The cloud point was found to be range of 40-50^{0}C for all formulation. Incorporation of drug had very little effect on the cloud point,. Such a result can conclude that a stable emulsion of nimorazole can be formed at physiological temperature in vivo, the result indicated in table 5.

3.9 Effect of Drug Loading on Droplet Size

The effect of drug loading on particle size is indicated in table 5 and 6. Addition of drug increased the particle size significantly.This may be because the drug loaded increased the weight ratio of the oil phase thus less amount of surfactant was available to reduce the size of the particle. Similar trend of result were observed by Wei Wu et al.(2006[12]) and Nagarsenker et al.(2007[9]).

Table 5: Evaluation of the selected formulation using Pluronic68-Pluronic 127 surfactant combination without drug

Evaluation parameter	F1(1:1)	F2(0.5:1.5)	F3(1.5:0.5)
Particle size(µm)	1.662	0.876	1.666
Polydispersity index	0.125	0.733	0.513
ζ potential(mV)	-16.56	-8.32	-18.16
Refractive index	1.35	1.36	1.34

Table 6: Evaluation of the selected formulation using Pluronic F 68-Pluronic F 127 surfactant combination with drug

Evaluation parameter	S1	S2	S3	M1	M2	M3
Particle size(µm)	70.97	-	65.85	79.68	101.22	-
Polydispersity index	0.703	0.299	0.418	0.434	0.829	0.154
ζ potential(mV)	-11.58	-8.11	-17.12	-6..232	-8.7	-6.24
Refractive index	1.38	1.40	1.37	1.46	1.47	1.44
Cloud Point (without drug)^{0}C	44	48	46	40	42	39
Cloud Point (with drug)^{0}C	48	51	49	44	45	43

S1(1:1),S2(0.5:1.5),S3(1.5:0.5),(S-Solvent evaporation), M1(1:1),M2(0.5:1.5),M3(1.5:0.5),(M-Melt method)

3.10 Effect of Dilution in Different Media

The influence of increasing dilution (10,100 times) and change in diluents was evaluated on the behaviors of the formulations, the observation are depicted in forms of grades and are depicted in forms of grades and are indicated in the table 7. In all cases, increased dilution and change in diluents showed clear or bluish appearance, with no drug precipitation. This suggests that all the formulation were robust to dilution and change in diluents, thus maintaining their performance in vivo.

Table 7: Observations for Effect of dilution in different media on the formulation and thermodynamic stability study

Dilution media	S1	S2	S3	M1	M2	M3
1. Distill water						
a.10 times	II	II	I	I	II	I
b.100 times	I	I	I	II	I	I
2.Simulated Gastric fluid(SGF)						
a.10 times	II	I	I	II	I	I
b.100 times	I	I	I	I	I	I
3. Simulated Intestinal fluid(SIF)						
a.10 times	II	II	I	II	II	I
b.100 times	II	I	I	I	I	I
Thermodynamic Stability study						
a. Centrifugation						
Phase separation	X	X	X	X	X	X
Precipitation	X	X	X	X	X	X
b. Freeze thaw cycles						
20^{0}C	Hazy	Hazy	Hazy	Hazy	Hazy	Hazy
-40^{0}C	Clear	Hazy	Clear	Hazy	Hazy	Clear
RT	Clear	Hazy	Clear	Clear	Clear	Clear

3.11 Thermodynamic Stability Study

Thermodynamic stability study was performed to access the stability of the emulsion formed with the selected excipients and are indicated in Table 7. All the formulation showed good stability to various stress condition. None of the formulation showed phase separation or precipitation after centrifugation. Though formulations showed clear to hazy appearance at various storage condition.

3.12 Differential Scanning Colorimetry (DSC)

DSC curves of S-SEDDS-S3(A) and pure Nimorazole(B), Fig. 4. Pure Drug Nimorazole showed a sharp endothermic peak at about 109^{0}C corresponding to its melting point and indicating its crystalline nature. No obvious peak of the drug was found in the solid SEDDS–S3 indicating that the drug must be present molecularly dissolved state in solid SEDDS.

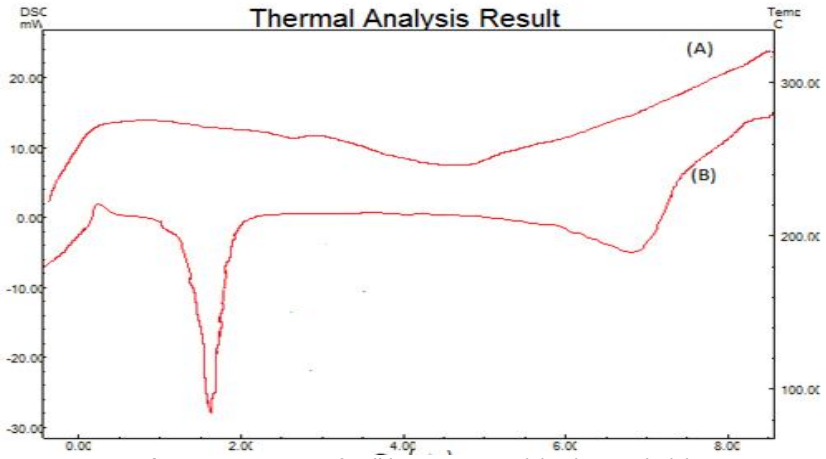

Fig. 2: DSC Spectra of Solid SMEDDS-S3 (A), Nimorazole (B)

3.13 Fourier Transfer Infra-red Spectroscopy

The pure drug Nimorazole exhibit characteristic peaks at 1552 cm^{-1} N-O asymmetric stretch,(C=C)stretching at 1452 cm^{-1}, (N-H)stretching at 1577 cm^{-1}The peaks at 1552, 1452 and 1577 cm^{-1}were disappeared and the drop in intensity of peaks at, 1615 and 1470cm^{-1} in S-SEDDS-S3 formulation indicate physical interaction (Fig.5). However the absence of extra peaks suggests that there was no possible chemical interaction between the drug and formulation ingredients and drug was properly dissolve in solvents.

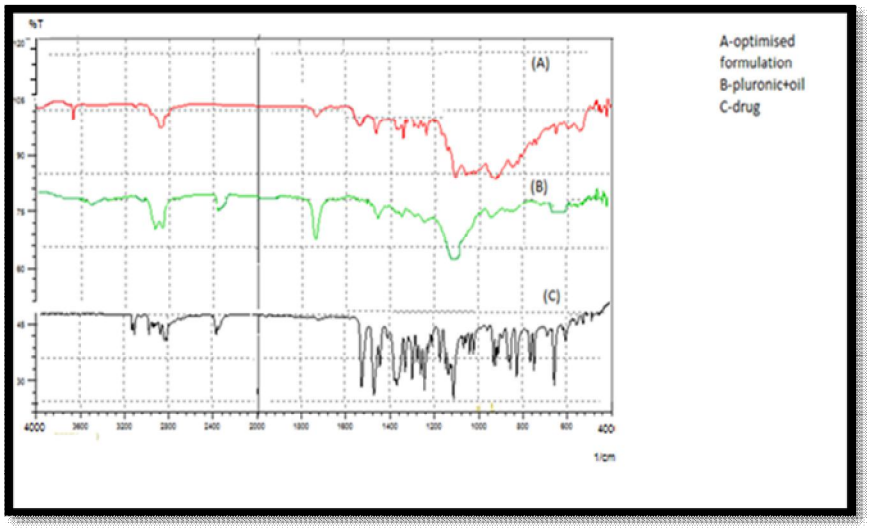

Fig. 3: FTIR spectra of A) Optimised formulation S-SMEDDS-S3 B) Pluronic + oil and C) Pure drug

3.14 Powder X-ray Diffractometry (XRD)

The powder X-ray diffractometry patterns are presented in Fig. 6. .Nimorazole had sharp peaks at the diffraction angles, showing a typical crystalline pattern. All of the major characteristic crystalline peaks for the drug and Optimised melt. S- SEDDS-S3 formulation showed peaks at diffraction angles, showing an amorphous pattern.Thus, like the DSC results, Nimorazole was present in a changed amorphous state in the SEDDS formulations prepared by solvent evaporation.

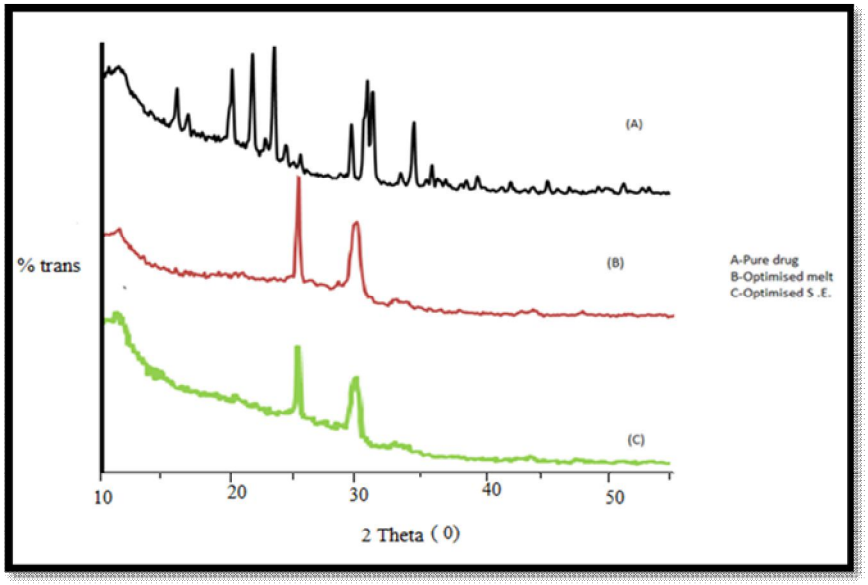

Fig. 4: XRD Spectra of Pure drug (A),Optimised melt(B)andOptimised S.E.(C)

3.15 Microscopic Examination

The results of the microscopic examination of solid preconcentrates are shown in Fig.7**.** Poloxamer is crystalline and form birefringent spherulites under the Digital Biological micro scope using1200 X 800 magnification, In melt method the irregular-needle shaped crystals of drug were observed might be due to polymeric transformation of drug on exposure to temperature, but these crystals on vortexing for 15-20 minutes disappeared. On the other hand, In Solvent evaporation method the liquid phase of Capmul PG 8 NF and drug was trapped in between the crystalline solid structure of Pluronic. Yellow fluorescence light used in scope to visualize the non-crystalline region of the system confirmed that the lipid along with drug is located between the crystalline domains of the steroyl polyoxyl glycerides.

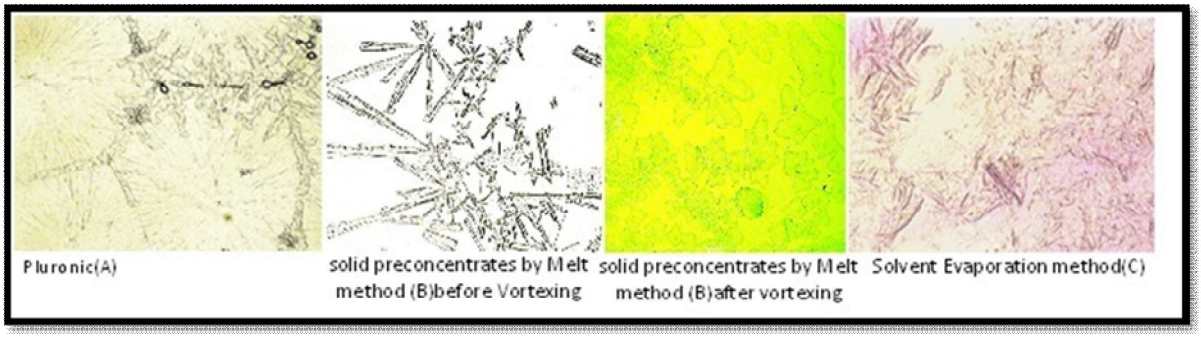

Fig. 5: microscopic examination of Pluronic (A), solid preconcentrates by Melt method (B) and Solvent Evaporation method(C)

4. CONCLUSION

From the present study it can be concluded that Capmul PG 8NF is suitable for the development of SEDDS formulation where liquid medium–chain triglyceride may be incorporated into the solid structure of Pluronic. Combination of Pluronic not only served as solidifying agent, there was also no need for a liquid co-surfactant. The potential for physical instability of the formulations due to the crystallization of the drug from the solid system was minimized as the drug remained dissolved in the lipid.The formulations may be filled into hard gelatin capsules in their molten state as they solidified as hard masses inside the capsules. The solid formulation formed very fine emulsions upon the dispersion in aqueous media.

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