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Design and Development of Oral Lipid Based Solid Self Micro emulsified Drug Delivery System

Shilpa P Chaudhari*[1], Sadhana Kolhe[1], A.A. Ranpise[1], M.P.Ratnaparkhi[1]

1.Marathwada Mitra Mandal's College of Pharmacy, Thergaon, Pune-33,University of Pune, Maharastra,India

ABSTRACT

The objective of the present study was to formulate a solid self micro emulsifying drug delivery system (SMEDDS) for oral administration to improve the solubility and bioavailability of Nimorazole. Solubility was determined in various oils, surfactants and cosurfactants. Of all the oils accessed for drug solubility, Capmul PG 8 NF showed higher solubility for drug and was better microemulsified using combination of Labrasol and Labrafac CC surfactant. The optimal formulation consists of 30% Capmul PG 8 NF, 50% Labrafac CC,20% Labrasol , was adsorbed on carriers Aerosil200, Microcrystalline cellulose (MCC) and Kaolin .The SMEDDS and solid SMEDDS were characterized for Percent transmittance (%T). 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. The solid SMEDDS are characterized by globule size analysis, and drug release studies of formulations are compared with plain drug. Adsorption on kaolin produced SMEDDS with the desired globule size and drug release. There was an increase in both the solubility and dissolution rate of drug in S-SMEDDS-K3 as compared to dissolution rate of pure Nimorazole.

Keyword: Solid self-microemulsifying drug delivery system ,% transmittance study, droplet size, Capmul PG 8 NF.

*Corresponding Author Email: shilpapchaudhari78@yahoo.com

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INTRODUCTION

Numerous potent lipophilic drugs shows the low oral bioavailability due to their poor aqueous solubility properties.[1] and the oral delivery of such drugs is frequently related to the low bioavailability, high intra- and inter- subject variability and a lack of dose proportionality[2]. Self micro emulsifying drug delivery systems are isotropic mixtures of oil, surfactant, co-surfactant and drug with a unique ability to form fine oil in water microemulsion upon mild agitation following dilution with aqueous phase.[3,4,5] Dissolution rate enhancement in the SMEDDS is due to the spontaneous formation of the emulsion in the gastrointestinal tract which presents the drug in solubilized form, and the droplet having small size which provides a large interfacial surface area for drug absorption.[6, 8] SEEDS provide a large interfacial area as compare to simple oily solutions which providing the partitioning of the drug between oil and water. The lipophilic drugs with dissolution-limited oral absorption, these systems provide an improvement in the rate and extent of absorption and more reproducible plasma concentration profiles..[7,8] The most accepted approach is the incorporation of the active lipophilic component into inert lipid vehicles[15], such as oils[16],surfactant dispersions, self-emulsifying formulations[17.18] ,emulsions and liposomess, with every formulation approach having its special advantages and limitations.

The major part of the formulations is Oils which play the vital role of maintaining the drug in solubilised form. SMEDDS are usually prepared in liquid state. So, the liquid SMEDDS are enclosed in hard or soft capsule to assist oral administration, but it produces some troubles such as stability, incompatibility, drug leakage and precipitation and capsule ageing. The SMEDDS incorporated into solid dosage forms is desirable but challenging.[9,10]

Adsorption to solid carriers is one the method to form solid SMEDDS. Free flowing powders may be obtained from liquid self emulsifying formulations by adsorption to solid carriers. The adsorption process is easy and simple which involved the addition of liquid formulation to carriers by mixing in a blender. The resulting powder then filled directly into the capsules Thus, S-SMEDDS combine the advantages of SMEDDS with those of solid dosage form e.g. low production cost, convenience of process control, better patient compliance and high stability [11,12]. Solid state characterization of S-SMEDDS is performed using SEM, DSC and powder x-ray diffractometry. Nimorazole (*N*-2-morpholinoethyl-5-nitroimidazole) having an antiprotozoal category which are effective in trichomonal infection [13] It has elimination half life of 2-4.8hrs. It is BCS class IV drug and very slightly soluble in water. It is also active against a wide range of pathogenic protozoa including Trichomonas vaginalis.[14]

The present research is an attempt to solve solubility and bioavailability problems of BCS class IV drug Nimorazole. Therefore the main objective of the study was to develop and evaluate optimized solid SMEDDS formulations containing Capmul PG 8NF as an oil and Labrafac cc and Labrasol used as a surfactant.

MATERIALS AND METHODS

Nimorazole was received as a gift from Lupin research park, Capmul PG 8 NF , Capmul MCM, Captex200, Captex300,Captex355 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.

Drug solubility determination

Solubility studies were conducted by placing an excess amount of Nimorazole(approximately 100 mg) in a vial containing 2 ml of the surfactants, and the mixture was mixed manually for ½ hr using a glass rod. After that mixture was placed for sonication for 2 hrs. Then mixture was allowed to equilibrate for 48hrs 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. The components were selected for further studies depending on the maximum drug solubility in oil, surfactant and co-surfactant.[20]

Preparation of self –microemulsifying formulation with selected oil

A series of SMEDDS preconcentrate were prepared compromising Capmul PG 8NF as an oil phase and using combination of Labrasol surfactant with Labrafac CC .Non-ionic surfactant combinations were examined at various ratios 0.25:0.75,0.5:0.5 and0.75:0.25.The samples were prepared using oil and surfactant combinations at ratios 7:3,6:4,1:1,4:6 and 3:7.Homogeneous mixtures of surfactant and oil at given weight ratio were blended in a glass vial for 10 min. These were then introduced into a 500ml measuring cylinder containing 100ml of distilled water, pre-equilibrated at 30^0C.The measuring cylinder was then inverted (rocked) once to provide minimum amount of shear for self-emulsification/dispersion. 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 formulation) using double distilled water as blank. Higher value of %T denotes formation of transparent system and thus help in denoting the formed microemulsion. So this technique was used instead of

pseudoternary phase diagram where visual observation is made and thus are chances of human error. Those SMEDDS preconcentrate dispersion showing higher %T value were selected for further evaluation.

Experimental design optimization of nimorazole-loaded SMEDDS

Firstly select the best suitable oil, surfactant and co-surfactant 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 SMEDDS of Nimorazole is given as per Table 1and 2. Oil and surfactant mixture was added, shake for 30 min for solubilization. The formulations were observed for isotropicity and were stored at room temperature for further evaluation. Factorial design was constructed to estimate the best amount of Nimorazole in SMEDDS, 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.[19]

In all the formulations drug Nimorazole (300mg) kept constant, Depending upon these ranges the fifteen formulations were formulated as per experimental design.

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 Micro Emulsifying Drug Delivery System (SMEDDS) of Nimorazole

Sr.	Oil (CapmulPG8NF)	F.C	F.C S:Co-s (C)(0.25+0.75)	F.C	S:Co-s (A)(0.5:0.5)	F.C	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%

Characterization and evaluation of the selected formation

Evaluation of liquid SMEDDS by ease of emulsification

The transmittance was determined for mixture with drug loading. The mixture, 50 mg equivalent of drug, was accurately weighed and diluted to 50 ml with double distilled water to yield fine emulsion. The ease of formation of emulsions was noted by noting the number of flask inversions required to give uniform emulsion. The resulting emulsions were observed visually for the relative turbidity. The emulsions were allowed to stand for 2 hr and their transmittance were measured by UV-double beam spectrophotometer 1800 (Shimadzu) using distilled water as blank.

Cloud point measurement

Cloud point temperatures (Tc) were determined by visual observation. 0.5 mL 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.

Effect of drug loading on droplet size

Effect of drug loading on globule size of micro-emulsion was studied using optimized composition formulation were prepared with or without Nimorazole.The resultant SMEDDS preconcentrate, 0.5 mL was diluted to 100 mL with double distill water and the mean globule size of the resulting micro-emulsion was determined by Motic digital Microscope(model:UMWBL-233ASC,Mumbai).

Effect of dilution in different media

Dilution study was done to access the effect of dilution on SMEDDS preconcentrate, in order to mimic physiological dilution process after oral administration. In this study selected formulation were subjected to increasing dilution (i.e. 10 and 100times) 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.

Thermodynamic stability study

The objective of thermodynamic stability is to evaluate the phase separation and effect of temperature variation on SMEDDS formulation nimorazole SMEDDS 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.

Characterization and evaluation of the optimized formulation

Determination of droplet size and polydispersity index

The globule size determination as performed using photon correlation spectroscopy within built zetasizer (model: nano zs, malvern instrument, west borough, MA, USA) Aliquot preconcentrate (0.5 mL) was diluted to 50mL with distill water; stir slowly to form a dispersion. Diluted samples were directly placed into the module for measurements. Measurements are made in triplicate.

Zeta potential determination

SMEDDS (0.5mL) was diluted to 50 mL with distill water in glass beaker with constant stirring. Zeta potential of the resultant microemulsion was determined using the zeta sizer (model: nano zs, Malvern instrument, west borough, MA, USA). All determination were made in triplicate.

Refractive index determination

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

***In vitro* dissolution studies in 0.1N HCL**

In vitro dissolution of liquid SMEDDS formulations was carried out by using dissolution test apparatus USP XXII (paddle type).The liquid SMEDDS 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 5ml 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 maximum of 297nm by using Shimadzu UV-1800 spectrophotometer.21

Preparation of solid SMEDDS formulation

For the preparation of solid SMEDDS the optimized formulation of liquid SMEDDS (L15) formulation containing Capmul PG 8 NF (30%),0.75:0.25 ratio of surfactant and co-surfactants i.e. Labrafac CC (50%) and Labrasol (20%) in a glass vial was mixed with solid carriers. Microcrystalline cellulose (MCC) ,Kaolin and Aerosil 200 were used as solid adsorbent carriers. Carriers: SMEDDS were varied as different ratios 0.25:1, 0.5:1, 0.75:1.Then the SMEDDS (A1-0.25:1,A2-0.5:1,A3-0.75:1) (A-Aerosil, B-MMC, C –Kaolin) formulation was added drop wise over the solid adsorbent contained in a porcelain dish. 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.

Evaluation of solid SMEDDS

Globule size analysis

Globule size of the microemulsion formed after dispersions of solid-SMEDDS was determined by Motic microscope.

Drug release studies in 0.1N HCL

In vitro dissolution of solid SMEDDS of Aerosil200 and M.C.C formulations was carried out by using dissolution test apparatus USP XXII (paddle type).The solid SMEDDS 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. Same quantity of fresh fluid 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.

Solid state characterization of solid SMEDDS

Interaction study by FTIR

FT-IR spectra of Nimorazole (drug), Kaolin(adsorbent), prepared S-SMEDDS-K3 and Labrasol Labrafac cc mixture were recorded on Shimadzu FTIR- 8400 spectrophotometer. Sample was placed in sample holder; the scanning was performed between 4000 $cm^{-1}$to 400 cm^{-1}range.[22]

Differential scanning calorimetry (DSC)

The molecular state of the drug in S-SMEDDS-K3 formulation was evaluated by performing DSC analysis of pure drug and S-SEDDS-K3. The DSC curves of the samples were obtained by a differential scanning calorimeter**.** The samples (about 3.00mg) were placed in standard aluminum pans, and dry nitrogen was used as effluent gas. All samples were scanned at a temperature ramp speed of 5^0C/min and the heat flow from 0-280.[11]

X-ray powder diffraction

The PXRD patterns of pure drug and S-SEDDS-K3 formulation were obtained using X-ray diffractometer (X' Pert PRO PA Analytical, Netherlands).[23]

Morphological analysis of s-SMEDDS by SEM

The surface morphology of the kaolin and S-SEDDS-K3formulation was investigated by scanning electron microscope (SEM) (S-4100, Hitachi, Japan).Samples were fixed on a brass stub using double sided adhesive tape and were made electrically conductive by coating with a thin layer of gold and SEM images were recorded at 15 kev accelerating voltage.[10]

Drug release studies in 0.1N HCL

In vitro dissolution of solid SMEDDS of Aerosil200, MCC and Kaolin formulations was carried out by using dissolution test apparatus USP XXII (paddle type).The solid SMEDDS 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 50rpm. An aliquot of 5 ml was withdrawn by means of a pipette at predetermined intervals. Same quantity of fresh fluid was replaced to maintain apparent sink conditions inside the dissolution compartments. The aliquots were assayed spectrophotometrically at a maximum of 267 nm by using Shimadzu UV-1800 spectrophotometer.

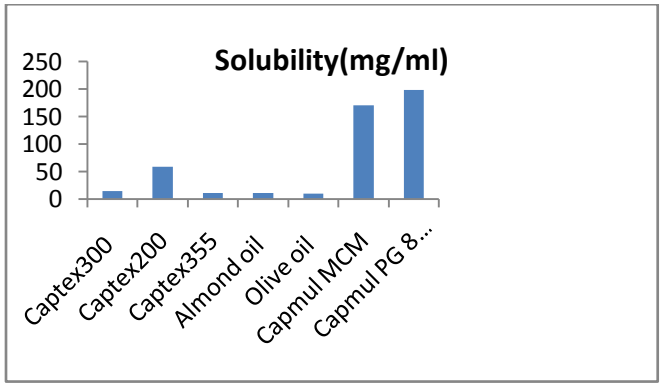
Grade- dispensability and appearance

- Grade I- Rapid forming microemulsion, 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

RESULTS AND DISCUSSION

Drug solubility determination

Solubility of nimorazole in various oils and surfactants and is indicated in Figure1 and 2. 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 while drug solubility in surfactants was found in decreasing order Labrafac CC >Labrasol >Tween 80. Drug solubility was due to the caprylic acid in the oil. 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% respectively; data provided by the manufacturer) Also drug solubility in surfactant was higher for Labrafac CC, The reason for such a behavior may be attributed to the Caprylic acid making it more favorable to solubilized poorly water-soluble drug. Capmul PG 8 NF was selected as oil phase and Labrafac CC as surfactant and Labrasol as co-surfactant were selected for further study.



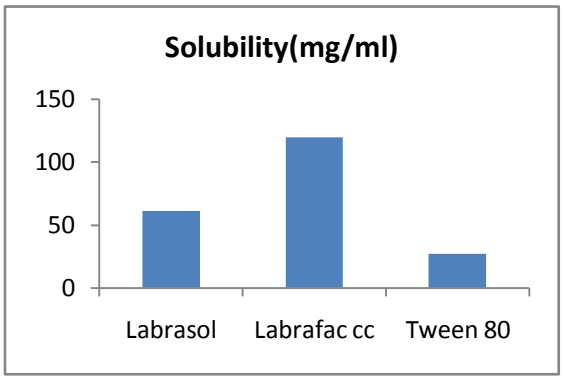


Figure 1:Solubility of drug in different oils Figure 2:Solubility of drug in diff.surfactant

Optimization

The statistically significant relationship between the dependent and independent variables are constructed based on the ANOVA results (Table 3). The effect of surfactant: co- surfactant ratio (X1)and concentration (X2) when droplet size (Y1) is considered as response Figure 3(A). 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. Increasing the surfactant to co-surfactant concentration shows decrease in the droplet size. Figure 3(B) shows the surface response plot of surfactant: cosurfactant ratio and concentration when cumulative amount of Nimorazole release after 15 min from SMEDDS is considered as the response. 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. Figure (C) shows the surface response plot for % transmission. From the obtained results it can be concluded that an optimal Nimorazole-loaded SMEDDS formulation may be composed of Capmul PG 8 NF (20%), Labrafac CC(50%) and Labrasol (20%) that is L15 formulation.

Table 3: 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	29.41	0.0001	0.9566	0.9241	0.8475	2.42	Suggested
Y_2(Droplet size)	2F1	0.020	0.0001	0.9495	0.9117	0.8225	0.028	Suggested
Y_3(% transmission)	2F1	314.87	0.0001	0.9921	0.9820	0.9823	1.53	Suggested

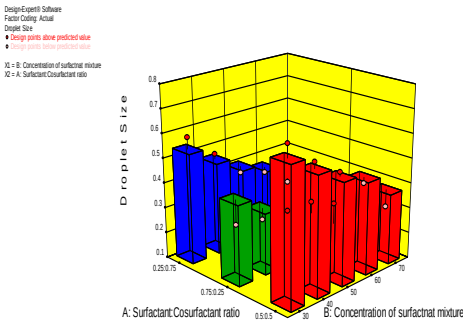
Equation: $Y1=A_0+A_1X_1+A_2X_2+A_3X_3+A_{12}X_1X_2+A_{13}X_1X_3+A_{23}X_2X_3$

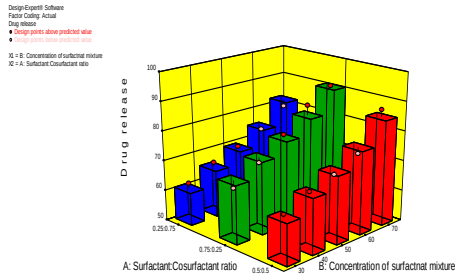
(a)Droplet size $Y1=0.32+0.082X_1-0.081X_2+0.10X_3+0.040X_1X_2-0.045X_1X_3-0.060X_2X_3$

(b)% Drug release $Y2=76.32-3.34X_1+8.61X_2-2.46X_3-6.34X_1X_2-2.98X_1X_3+2.18X_2X_3$

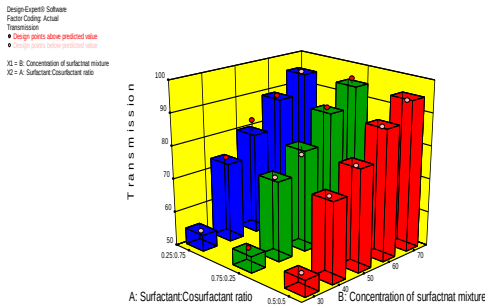
% Transmission

(c)$Y3=78.90-23.95X_1-4.74X_2+1.76X_3+10.50X_1X_2$





(A)Response surface plot for Droplet size **(B) Response surface plot for Drug release**



(C) Response surface plot for % Transmission

In transmission study the %T versus surfactant concentration were plotted to denote the system which disperse into a microemulsion, Higher value of %T denotes that the system has small globule size and thus less scattering. Emulsifying capacity was studied with different ratios of Labrafac CC as primary surfactant and Labrasol as a secondary surfactant. %T values increased as the ratio of surfactant: co-surfactant increased, indicating the effect of different ratios of surfactants in formation of microemulsion. Enhanced capacity was observed for 0.75:0.25 ratio of surfactant as compare to other ratio.

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. The smaller the globule size, larger the surface area provided for drug absorption. From all the formulation batches, the globule size of resulting microemulsion was lowest for formulation L15. The average size of the resultant emulsion after dilution was found to be 0.158µm, 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.

Dissolution studies were performed for SMEDDS containing 300 mg Nimorazole. The release of nimorazole from these formulation was evaluated . The L15 Formulation showed rapid release of

the drug as compared to the other formulation. Such a result can be attributed to the reduced particle size and increase in the fluidity of the dispersion due to incorporation Labrasol as secondary surfactant.

Evaluation of liquid SMEDDS

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, as shown in table 4. Such a result can conclude that a stable microemulsion of nimorazole can be formed at physiological temperature in vivo.

Table 4:Cloud point measurement

Formulation code	Cloud Point (without drug)^{0}C	Cloud Point (with drug)^{0}C
L5	44	48
L10	48	51
L15	46	49

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 indicated in the table 5. 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.

Thermodynamic stability study

Thermodynamic stability study was performed to access the stability of the microemulsion formed with the selected excipients and are indicated in Table 5. 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.

Table 5: Observation for effect of dilution in different media on the formulation and thermodynamic stability study

Dilution media	L5	L10	L15
1.Distill water			
a.10 times	II	II	II
b.100 times	I	I	II
2.Simulated Gastric fluid(SGF)			
a. 10 times	I	I	II
b.100 times	I	I	II
3.Simulated Intestinal fluid(SIF)			
a. 10 times	I	I	II

b.100 times	I	I	II
Thermodynamic Stability study			
a. Centrifugation			
Phase separation	X	X	X
Precipitation	X	X	X
b.Freeze thaw cycles			
20^0C	Hazy	Hazy	Hazy
-40^0C	Clear	Hazy	Clear
RT	Clear	Hazy	Clear

Characterization and evaluation of the optimized formulation

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

Table 6:Evaluation of the selected formulation with and without drug

	Without drug	**With drug**
Evaluation parameter	L15	L15
Particle size	0.992	1.903
Polydispersity index	0.359	0.257
ζ potential(mV)	-12.47	-28.59
Refractive index	1.34	1.37

Mean particle size and polydispersity index 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 microemulsion droplets preventing the coalescence droplets and increase in the stability.

Refractive index

There was no significant difference in the refractive index values of the formulation tested. The refractive index close to that of water prove the isotropicity of the system.

Effect of drug loading on droplet size

The effect of drug loading on particle size is indicated in table 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]

Solid state characterization of solid SMEDDS

FT-IR studies

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}(Figure 4.D). 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-SMEDDS-K3 formulation indicate physical interaction (Figure4.A).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.

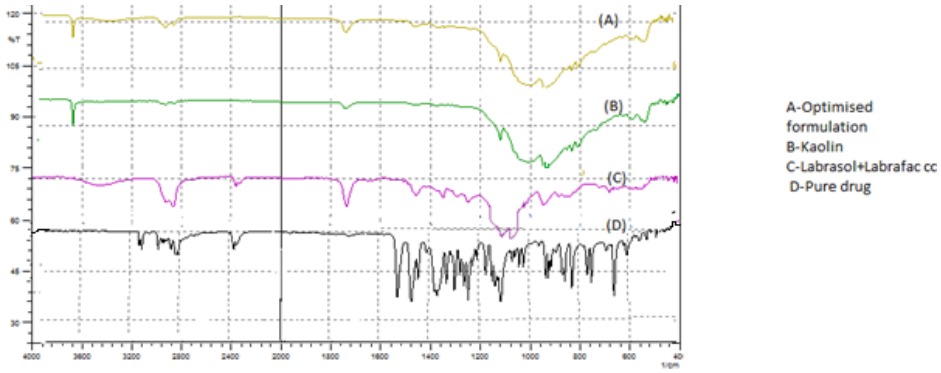


Figure 4:FTIR spectra of A) Optimized formulation S-SMEDDS-K3 B)Kaolin C)Labrasol+Labrafac CC D)Pure drug

X-ray powder diffraction

The powder X-ray diffractometry patterns are presented in Figure 5.Nimorazole had sharp peaks at the diffraction angles, showing a typical crystalline pattern (Figure.5A). S-SMEDDS-K3formulation showed peaks at diffraction angles, showing an amorphous pattern(Figure.5B).Thus, like the DSC results, Nimorazole was present in a changed amorphous state in the SMEDDS formulations prepared with Kaolin.

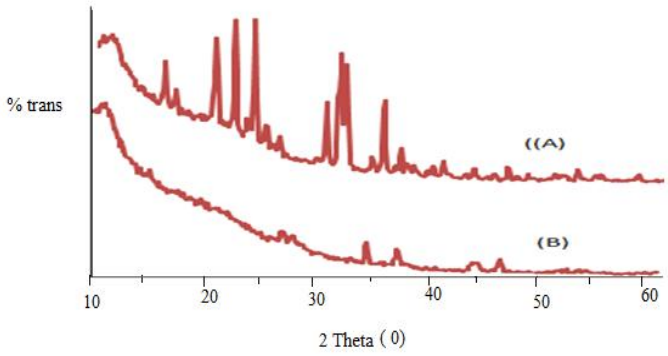


Figure 5:XRD pattern of A) Pure drug B) S-SMEDDS-K3

DSC

DSC curves of pure Nimorazole and S-SMEDDS-K3 are shown in Figure.6 Pure Nimorazole showed a sharp endothermic peak at about 109 ^{0}C corresponding to its melting point and

indicating its crystalline nature (Figure 6B). No obvious peak of the drug was found in the solid SMEDDS–K3 (Figure 6A)indicating that the drug must be present molecularly dissolved state in solid SMEDDS

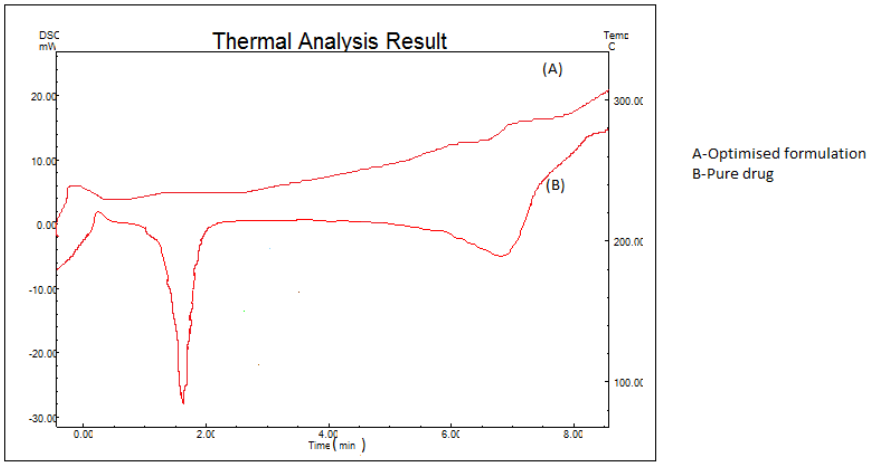
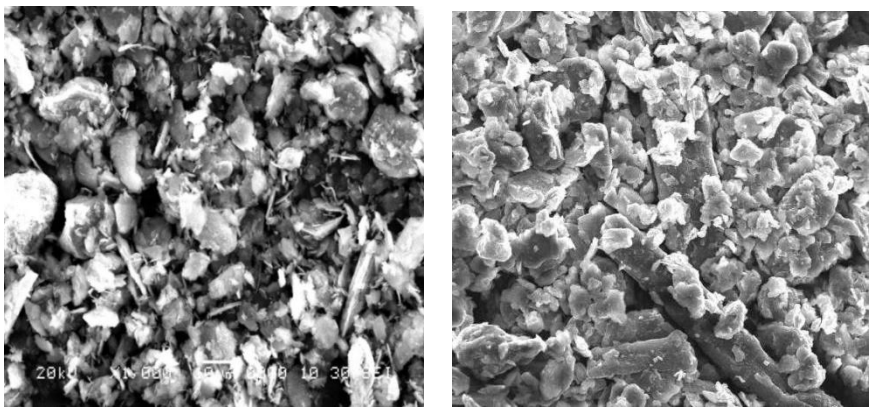


Figure 6:DSC of A)Optimized formulation (S-SMEDDS-K3) B) Pure drug

Morphological analysis of solid SMEDDS

The scanning electron micrographs of Kaolin and solid SMEDDS are shown in Figure7.Kaolin (Figure.7A) appeared with a rough surface with porous particles. However, the solid SMEDDS (Figure.7B) appeared as smooth-surfaced Kaolin particles, indicating that the liquid SMEDDS is absorbed or coated inside the pores of Kaolin.



(A) **(B)**

Figure 7:Scanning electron micrographs: (A) Kaolin; (B) solid SMEDDS -K3

***In vitro* dissolution test**

In the self-emulsifying systems, the free energy required to form an emulsion was very low, thereby allowing spontaneous formation of an interface between the oil droplets and water. It suggested that the oil/surfactant/cosurfactant and water phases effectively swell, *In vitro* drug release studies were performed for solid SMEDDS of Aerosil 200, microcrystalline cellulose,

Kaolin and Nimorazole powder, (A1-0.25:1,A2-0.5:1,A3-0.75:1-A-Aerosil,M-MMC, K –Kaolin)and are profiled in figure 8.

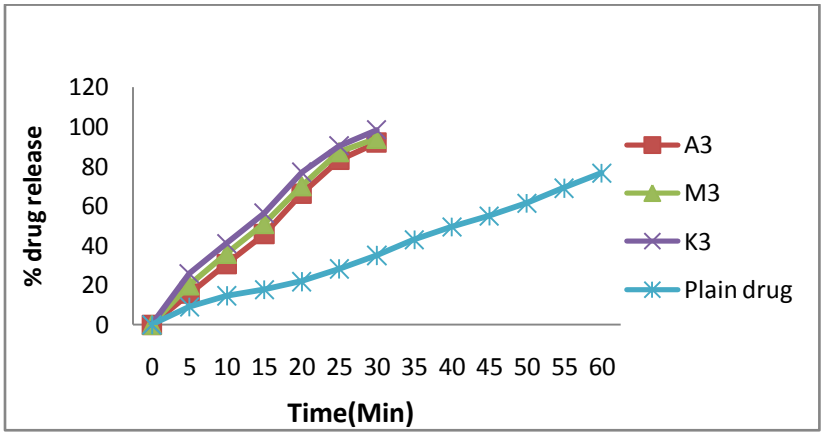


Figure 8: In vitro release of selected SMEDDS

CONCLUSION

From the whole study it was concluded that there was an increase in both the solubility and dissolution rate of drug in S-SMEDDS-K3 as compared to dissolution rate of pure Nimorazole. The significant increase in solubility and dissolution was observed in formulation S-SMEDDS K3.

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