AMERICAN JOURNAL OF PHARMTECH RESEARCH

Journal home page: http://www.ajptr.com/

Formulation and Evaluation of Solid Self Micro Emulsifying Drug Delivery System of Lamotrigine

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ABSTRACT

The objective of the present study was to formulate a solid self micro emulsifying of drug delivery system (SMEDDS) for oral administration to improve the solubility and bioavailability of Lamotrigine. Solubility was determined in various oils, surfactants and cosurfactants. Ternary phase diagrams were constructed to evaluate the micro emulsification existence area. The optimized formula is obtained by factorial design employed as statistical tool. The optimal formulation consists of 20% Capmul MCM C_8, 55% Labrasol , 25% Tween 80 was adsorbed on carriers Aerosil200, Microcrystalline cellulose (MCC) .The solid SMEDDS are characterized by globule size analysis, and drug release studies of formulations are compared with plain drug. The pharmacokinetic study in rats for the optimized formulation was performed and compared to plain drug powder. SMEDDS have significantly increased the *C*max and area under the curve (AUC) of Lamotrigine compared to powder ($P < 0.001$). Thus, this self-micro emulsifying drug delivery system should been effective oral dosage form for improving oral bioavailability of Lamotrigine.

Key Words: Solid self-microemulsifying drug delivery system, Globule size, Dissolution, Oral bioavailability

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Received 11 August 2012, Accepted 22 August 2012

Please cite this article in press as: Goli R *et al.*, Formulation and Evaluation of Solid Self Micro Emulsifying Drug Delivery System of Lamotrigine. American Journal of PharmTech Research 2012.

INTRODUCTION

Approximately 40% of new chemical entities exhibit poor aqueous solubility, oral delivery of such drugs presents a major challenge to drug formulators. This is because when they are administered orally the dissolution rate in gastrointestinal tract becomes the rate limiting step in the absorption and hence bioavailability from gastrointestine[1,2,3]. Low aqueous solubility will lead to poor oral absorption, high intra-inter subject variability and lack of dose proportionality. To overcome these problems various formulation various formulation strategies have been adopted[9, 4]. Lipid based formulations represent a solution to delivery of poorly soluble actives, among these lipid based systems self micro emulsifying drug delivery systems(SMEDDS) are considered as promising technology to improve the rate and extent of absorption of poorly water soluble drugs[13,17].SMEDDS formulations are isotropic mixtures of an oil, surfactant, cosurfactants and drug. The basic principle of this system is its ability to form fine o/w microemulsion under gentle agitation following dilution by aqueous phase[10, 16]. Thus spontaneous formation of an emulsion in gastrointestinal tract present the drug in solubilised form and the small size of the formed oil droplet and polarity of oil droplet promote faster drug release into aqueous phase[6].However traditional preparations of SMEDDS are usually prepared in liquid state. So, the liquid SMEDDS are enclosed in hard or soft capsule to facilitate oral administration, but it produces some disadvantages such as stability, incompatibility, drug leakage and precipitation and capsule ageing. The incorporation of SMEDDS into solid dosage forms is desirable but challenging.[7, 11].

Adsorption to solid carriers is one the technique to form solid SMEDDS. Free flowing powders may be obtained from liquid self emulsifying formulations by adsorption to solid carriers. The adsorption process is simple and involved addition of liquid formulation to carriers by mixing in a blender. The resulting powder then filled directly in to capsules. A significant benefit of adsorbent technique is good content uniformity. SMEDDS can be adsorbed at high levels up to 70%w/w on to suitable carriers[7, 8].

Lamotrigine [6-(2, 3-dichlorophenyl)-1, 2, 4-triazine-3, 5-diamine] is an antiepileptic agent shown to be effective in adjunctive treatment for refractory partial seizures and generalized seizures. It has elimination half life of 24hrs .It is BCS class2 drug and very slightly soluble in water (0.17mg/ml). It works by inhibiting voltage dependent sodium channels, resulting in decreased release of excitatory neurotransmitters glutamate and aspartate[12].This has lead to the idea of formulating Lamotrigine as SMEDDS in an attempt to solve its solubility and

bioavailability problems. Therefore the main objective of the study was to develop and evaluate optimized SMEDDS formulations to improve the dissolution rate and bioavailability of drug[15].

MATERIALS AND METHODS

Materials

Lamotrigine was obtained as a gift sample from Kopran Pharmaceuticals (Mumbai). Diesters of caprylic/capric acids (Captex 200) and C8/C9 mono/diglycerides (Capmul MCM C_8) were generous gifts from Abitec Corp. Labrasol was kindly provided as a gift sample by Mylan Laboratories. Tween 80, Tween 20, Span 20, Span 80, Tween 60 and (all AR grade) were purchased from Loba Chemicals.

Solubility Studies

The equilibrium solubility of Lamotrigine in various oils, surfactants and cosurfactants was determined. Briefly, an excess amount of Lamotrigine was added to each glass vial containing 2ml of oil or surfactant or cosurfactants. Then the drug was mixed manually for 1/2hr, after that vials are kept in sonicator for 2hrs.Glass vials were then kept in water bath for 48hrs for reaching the equilibrium. After 48hrs these vials are centrifuged at 3000rpm for 20min and the amount of drug dissolved was determined by diluting the supernatant in methanol by using UV-spectrophotometer .The components were selected for further studies depending on the maximum drug solubility in oil, surfactant and co-surfactant[17].

Solubility determination of Lamotrigine in different ratios of selected oils, surfactants and cosurfactants

Two ml of selected oil, surfactant and co-surfactant were taken in1:9 to 9:1 ratios and added in glass vial containing excess amount of drug. Then the drug was mixed manually for 1/2hr, after that vials are kept in sonicator for 2hrs.Glass vials were then kept in water bath for 48hrs for reaching equilibrium. After 48hrs these vials are centrifuged at 3000rpm for 20min and the amount of drug dissolved was determined by diluting the supernatant in methanol by using UV-spectrophotometer[17].

Construction of pseudo-ternary phase diagrams

The pseudo-ternary phase diagrams were constructed by titration of homogenous liquid mixture of oil, surfactant and cosurfactants with water at room temperature. On the basis of solubility studies CapmulMCM selected as oil phase, Labrasol as surfactant and Tween80 as cosurfactants. Oil, surfactant and cosurfactants are grouped in to three groups for phase studies. Surfactant and Cosurfactant in each group were mixed in different weight ratio(0.5:0.5,0.75:0.25,0.25:0.75).For each phase diagram oil and specific surfactant mixture ratio are mixed thoroughly in different

weight ratio from 1:9 to 9:1 (1:9,2:8,3:7,4:6,5:5,6:4,7:3,8:2,9:1) in different vials. Each mixture was then slowly titrated with aliquots of distilled water and stirred at room temperature to attain equilibrium. The mixture was visually examined for transparency .Clear and isotropic mixtures are deemed to be within microemulsion region[9].

Experimental design optimization of Lamotrigine-loaded SMEDDS

After selecting 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 Lamotrigine is given as per Table1.

Oil and surfactant mixture are added as given in Table1, warmed on water bath at 40^0C 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 Lamotrigine in SMEDDS, with combinations from two factors (independent variables) which were surfactant: cosurfactant ratio(x_1) and concentrations(x_2).Droplet size (y_1), drug release (y_2) were dependent variables. The responses of model formulations were treated by Design-Expert® version 8.0.7.1 software[19].

Table 1a: Variables in Optimization Study

Variables	Factor
Independent	
X1	Surfactant: cosurfactant Ratio (+1(B), 0(A), -1(C))
X2	Concentration of surfactant mixture (10%- 90%)
Dependent	
Y1	Droplet size
Y2	Drug release

Table 1b: Composition of Self Micro Emulsifying Drug Delivery System (SMEDDS) of Lamotrigine

Sr.	Oil (CapmulMCM)	F.C	S:Co-s (A) (0.5:0.5)	F.C	S:Co-s(B) (0.75:0.25)	F.C	S:Co-s (C) (0.25+0.75)
1	90%	A1	10%	B1	10%	C1	10%
2	80%	A2	20%	B2	20%	C2	20%
3	70%	A3	30%	B3	30%	C3	30%
4	60%	A4	40%	B4	40%	C4	40%
5	50%	A5	50%	B5	50%	C5	50%
6	40%	A6	60%	B6	60%	C6	60%
7	30%	A7	70%	B7	70%	C7	70%
8	20%	A8	80%	B8	80%	C8	80%
9	10%	A9	90%	B9	90%	C9	90%

In all the formulations drug Lamotrigine (25mg) kept constant

Here F.C=Formulation code, S=Surfactant (Labrasol), Co-s=Cosurfactant (Tween80)

Depending upon these ranges the twenty seven formulations were formulated as per experimental design.

Evaluation of liquid SMEDDS

Phase separation study:

Each Liquid SMEDDS formulation (0.05ml) was added to 100 ml volumetric flask and diluted with 0.1 N HCl and distilled water up to the mark. After inverting volumetric flask for 3-4 times, each mixture was stored for 2h and phase separation was observed visually.

Evaluation of liquid SMEDDS by ease of emulsification

The transmittance was determined for mixture with drug loading. The mixture, 50 mg, 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 h and their transmittance were measured by UV-double beam spectrophotometer 1800 (Shimadzu) using distilled water as blank.

Globule size determination

Globule size was determined by Motic microscope (UMWBL-233ASC, Mumbai) for all the twenty seven formulations with drug. A 0.5ml of the homogeneous mixture was measured and diluted up to 100 ml with distilled water in beaker of 100 ml. Then beaker was placed on magnetic stirrer for 15 min. Then samples were taken for globule size determination.

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 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 267 nm by using Shimadzu UV-1800 spectrophotometer[14].

Preparation of solid SMEDDS formulation

For the preparation of solid SMEDDS the optimized formulation of liquid SMEDDS (B8) formulation containing Capmul MCM (20%),0.75:0.25 ratio of surfactant and cosurfactants i.e., Labrasol (55%) and Tween80 (25%) in a glass vial was mixed with solid carriers.

Microcrystalline cellulose (MCC) and Aerosil 200 were used as solid adsorbent carriers. Carriers: SMEDDS were varied as different ratios 0.25:1, 0.5:1, 1:1.Then the SMEDDS 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 267 nm by using Shimadzu UV-1800 spectrophotometer[9].

Solid state characterization of solid SMEDDS

Interaction study by FT-IR

FT-IR spectra of Lamotrigine (drug), Aerosil 200 (adsorbent), prepared S-SMEDDS-A2 and physical mixture of (drug & adsorbent) 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[4].

Differential Scanning Calorimetry (DSC)

The molecular state of the drug in S-SMEDDS-A2 formulation was evaluated by performing DSC analysis of pure drug, Aerosil200 and S-SEDDS-A2 and physical mixture. The DSC curves of the samples were obtained by a differential scanning calorimeter**.** 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 ramp speed of 5^0C/min and the heat flow from 0-280^0C [8].

X-ray powder diffraction

The PXRD patterns of pure drug, Aerosil200, physical mixture and S-SEDDS-A2 formulation

were obtained using X-ray diffractometer (X' Pert PRO PANalytical, Netherlands). The measuring conditions were as follows: CuKα radiation, nickel filtered; graphite monochromator; 45 kV voltages; and 40 mA current with X'celerator detector[9].

Morphological analysis of S-SMEDDS by SEM

The surface morphology of the pure drug, Aerosil200, physical mixture and S-SEDDS-A2 formulation 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[11].

In vivo study

Male albino wistar rats (180-200 g) used in the study had free access to food and water. Prior to the study the protocol has been approved by Institutional Animal Ethical Committee (IAEC 003/2012). Before dosing, the animals were kept for overnight fasting and were divided into two groups containing four in each group and were randomly administered with each treatment. Control group received an oral suspension of Lamotrigine (drug dispersed in 0.5% w/v of sodium carboxymethyl cellulose) and the test group was treated with S-SMEDDS-A2 dispersion at a dose of 10 mg/kg body weight. At predetermined time intervals, blood samples (500 µL) were collected from retro orbital plexus into micro-centrifuge tubes containing anticoagulant. Briefly, 200 µL of plasma sample was treated with 100 µL of methanol, 100 µL of 2.0 M sodium hydroxide solution and vortexed for 3 min. The mixture was extracted with 3 mL of ethyl acetate followed by centrifugation and the separated organic layer was dried. The residue was reconstituted with 100 µL of mobile phase and an aliquot of 20 µL was injected onto the HPLC. The calibration curve was constructed over a range of 0.1–15µg/mL in plasma (r^2 = 0.999) and validated.

The peak concentration (Cmax) and its time (Tmax) were obtained directly from the plasma concentration vs. time profile. The area under the curve (AUC_{0-t}) was calculated by using trapezoidal rule method. The $AUC_{t-\infty}$ was determined by dividing the plasma concentration at last time point with elimination rate constant (K). The relative bioavailability (F) was estimated by dividing the $AUC_{0-\infty}$ of S-SMEDDS-A2 formulation with control oral suspension. Student's *t*-tests were performed to evaluate the significant differences between the two formulations[18].

RESULTS AND DISCUSSION

Solubility studies

One important consideration when formulating a self emulsifying formulation is avoiding

precipitation of the drug. Therefore, the components used in the system should have high solubilization capacity for the drug, ensuring the solubilization of the drug in the resultant dispersion. Results of solubility studies are reported in Figure1&2.As seen from figure .1 capmul MCM C8 showed the highest solubilization capacity for Lamotrigine. Thus for our study we selected capmulMCM as oil, Labrasol as surfactant and Tween 80 as cosurfactants.

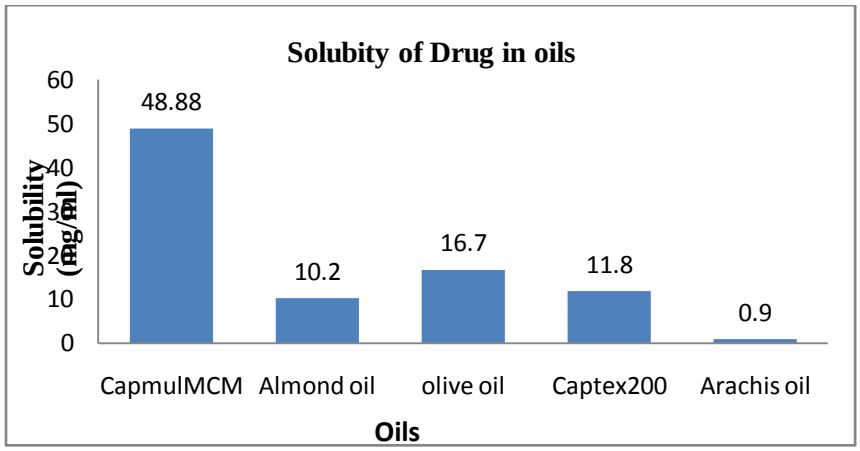

Figure 1: Solubility of drug in various oils

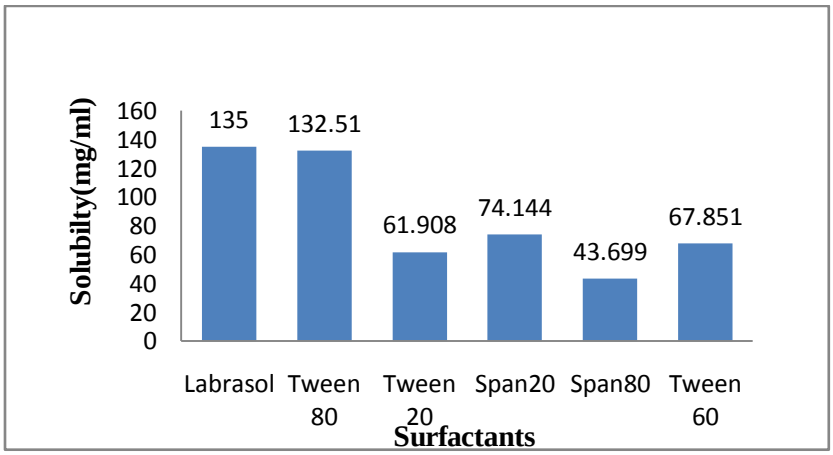

Figure 2: Solubility of drug in various surfactants

Solubility determination of Lamotrigine in different ratios of selected oils, surfactants and cosurfactants

Solubility of Lamotrigine also varied in the different combination of selected oil and surfactants. From results it was observed that solubility of Lamotrigine increases with increasing the concentration of surfactant in all the three cases but in 0.75:0.25 combination of Labrasol &Tween80 solubility was more as compared to other surfactant combinations.

Construction of pseudo-ternary phase diagrams

From ternary phase diagram it was observed that there was formation of almost same microemulsion region in all three types of SMEDDS without any significant difference, this

might be due to similar HLB values of both Labrasol and Tween80. Hence it was not possible to found out the best SMEDDS, which gives more microemulsion region, from ternary phase diagram construction (Figure 3, 4, 5).

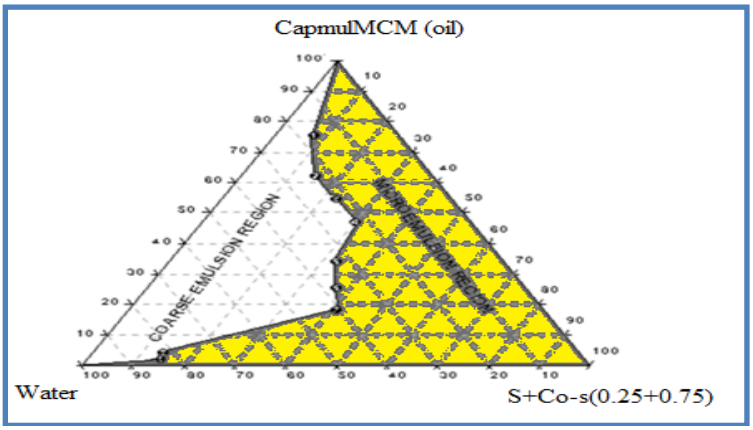

Figure 1 : Ternary phase diagram of Capmul (MCM) (Oil) and (0.25:0.75) ratio of Labrasol (surfactant) and Tween 80(cosurfactant)

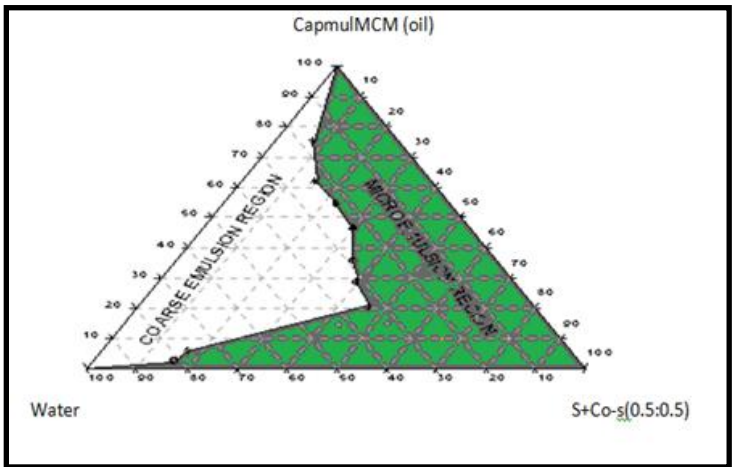

Figure 2: Ternary phase diagram of Capmul (MCM) (Oil) and (0.5:0.5) ratio of Labrasol (surfactant) and Tween 80(cosurfactants)

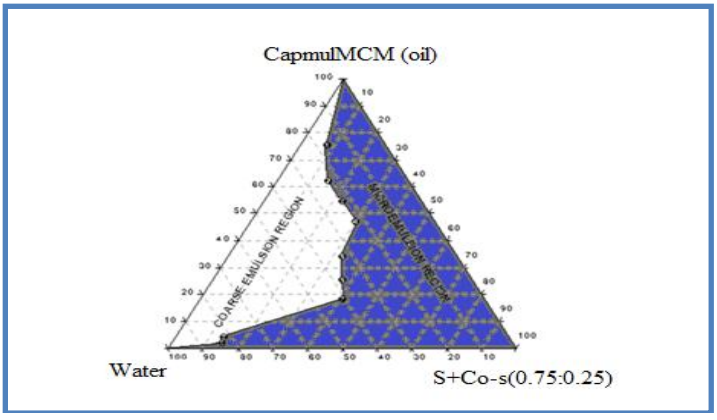

Figure 3: Ternary phase diagram of Capmul (MCM) (Oil) and (0.75:0.25) ratio of Labrasol (surfactant) and Tween 80(cosurfactant)

Evaluation of Liquid SMEDDS

Phase separation study

Phase separation study showed that all formulations subjected for this study were stable in 0.1N HCl & Distilled Water. No signs of phase separation within 2 hr, which implies formation of stable emulsion. Hence all formulations were subjected to further evaluation.

Emulsification ability

Transmittance study revealed that as the concentration of surfactant mixture ratio increases the transmittance of resulting emulsions increases. As the surfactant concentration increases the ease of emulsification also increases by getting increase in the transmittance. As the concentration of oil increases the transmittance as well as the ease of emulsification decreases. The transmittance of formulations was found less it may be due to least surfactant concentration this might be due to difference in CMC concentration of surfactant. Transmittance study gives only rough idea about the characteristics of resultant microemulsion. Thus transmittance of resulting emulsion is governed by surfactant and cosurfactant concentration.

Globule Size

It has been reported that 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 (Table 1), the globule size of resulting microemulsion was lowest for formulation B8. The average size of the resultant emulsion after dilution was found to be 52.8 nm, which was highly desirable, indicating that the system had narrow size. 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. This correlation exists up to certain extent.

***In vitro* dissolution test**

Drug release from the SMEDDS formulation (B8) was found to be significantly higher as compared with that of other formulations. It could be suggested that the SMEDDS formulation resulted in spontaneous formation of a microemulsion with a small droplet size, which permitted a faster rate of drug release into the aqueous phase, much faster than that of others. Thus, this greater availability of dissolved Lamotrigine from the SMEDDS formulation could lead to higher absorption and higher oral bioavailability. The maximum drug release was found to be 100.05±0.6 from the B8 formulation and results were shown in figure 7-9.

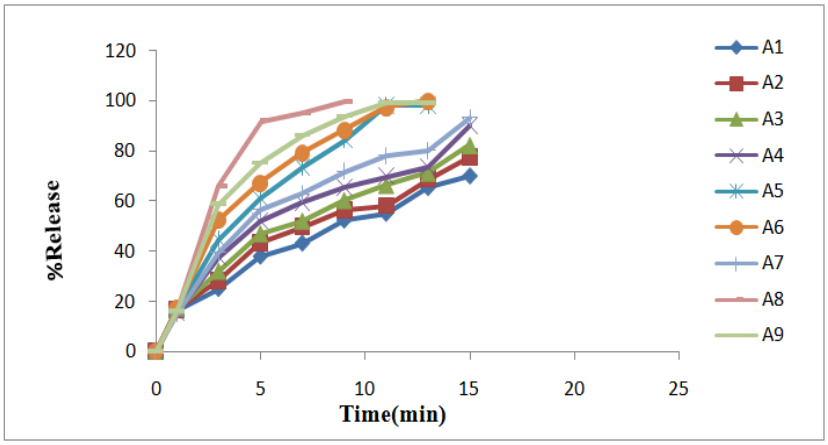

Figure 4: Dissolution profile of formulation A1- A9

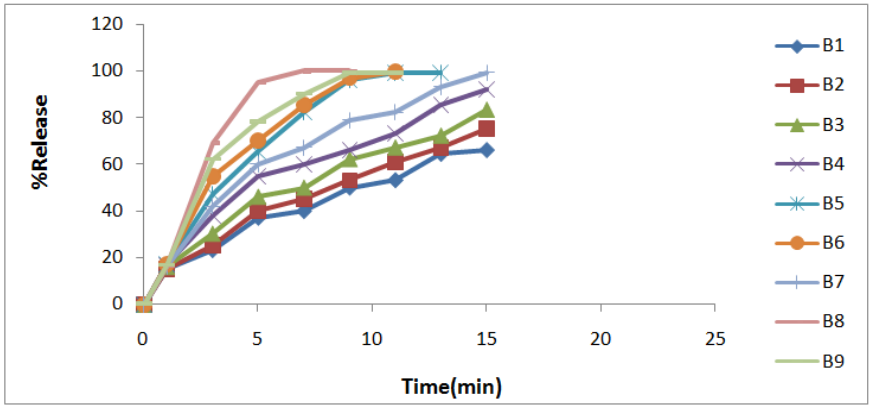

Figure 5: Dissolution profile of formulation B1- B9

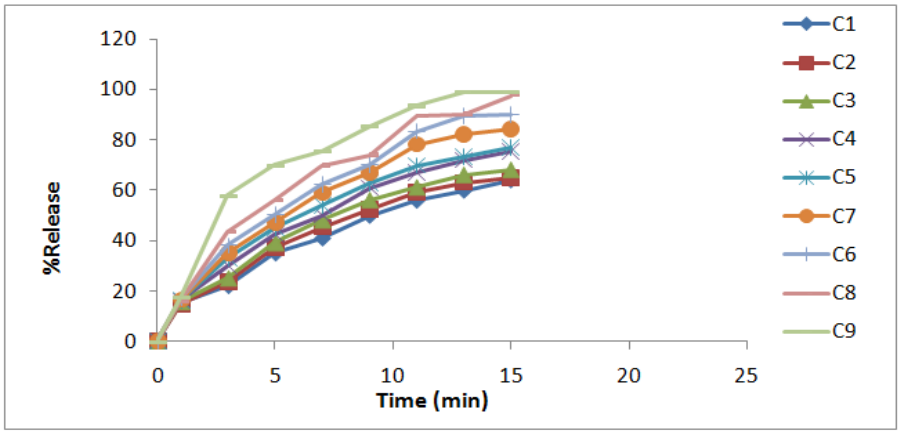

Figure 6: Dissolution profile of formulation C1- C9

Optimization

The statistically significant relationship between the dependent and independent variables are constructed based on the ANOVA results. The effect of surfactant: co- surfactant ratio (x_1) and

concentration range (x_2) when droplet size (y_1) is considered as response (figure 10). Change in the surfactant to co surfactant ratio shows change in the droplet size. Comparatively 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. The blue area represents the smallest droplet size which have maximum surfactant: co surfactant ratio (0.75:0.25) and concentration (80%).Figure 11 shows the surface response plot of surfactant: co surfactant ratio and concentration when cumulative amount of Lamotrigine release after 7 min from SMEDDS is considered as the response. The highest amount of Lamotrigine is released with maximum surfactant: co surfactant ratio and concentration. From the obtained results it can be concluded that an optimal Lamotrigine-loaded SMEDDS formulation may be composed of Capmul MCM-C8 (20%), Labrasol (55%) and Tween80 (25%) that is B8 formulation.

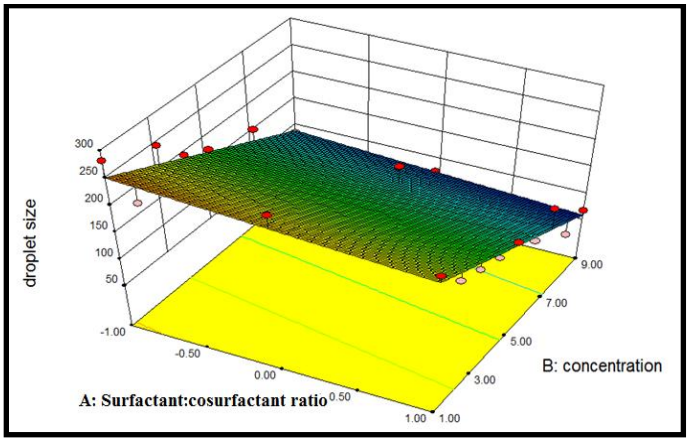

Figure 7: Response surface plot for Droplet size

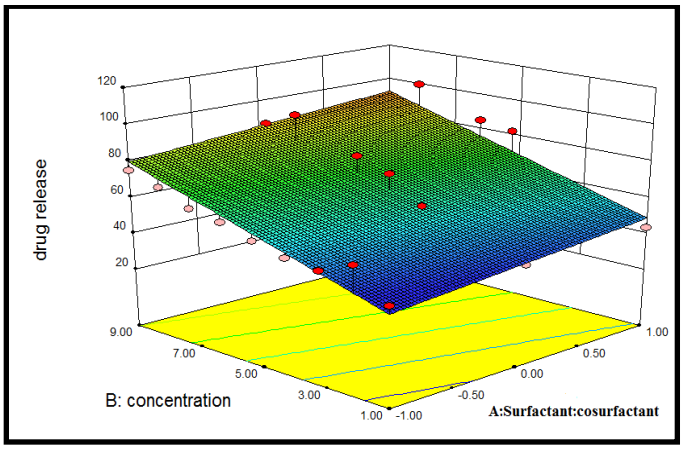

Figure 8 : Response surface plot for Drug release

Characterization of solid SMEDDS

From the prepared solid SMEDDS it was observed that 0.5:1 ratio of Aerosil200 (A2) and MCC (M2) showed uniform distribution and good flow properties, therefore these formulations are

kept for further evaluation.

Globule size analysis:

The average droplet sizes of both systems were less than 60 nm. The emulsion droplet size distribution in liquid and solid SMEDDS further confirmed the self-emulsification nature of the solid SMEDDS(figure 6)

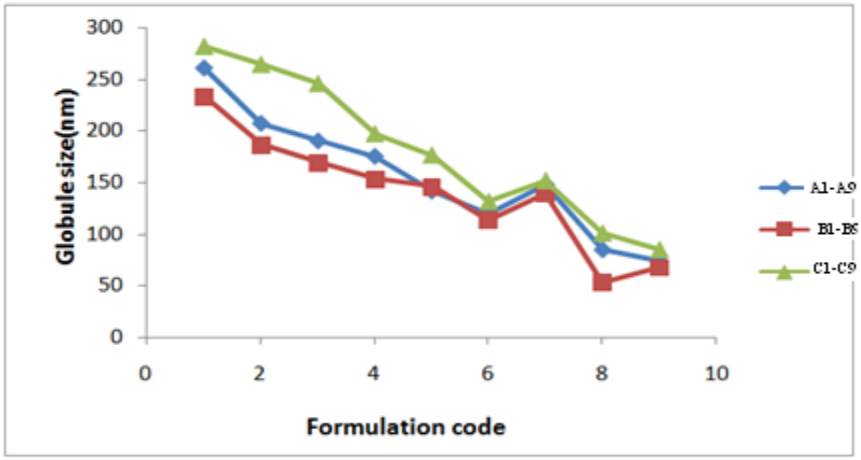

Figure 9 : Globule size of formulations -A1-A9, B1-B9, C1-C9.

***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 is suggested that the oil/surfactant/cosurfactant and water phases effectively swell, decrease the oil droplet size and eventually increase the release rate. *In vitro* drug release studies were performed for solid SMEDDS of Aerosil 200, microcrystalline cellulose and Lamotrigine powder, and are profiled in figure 12. It was observed that solid SMEDDS of Aerosil200 showed maximum drug release of 98% within 30 min compared with M.C.C and plain drug

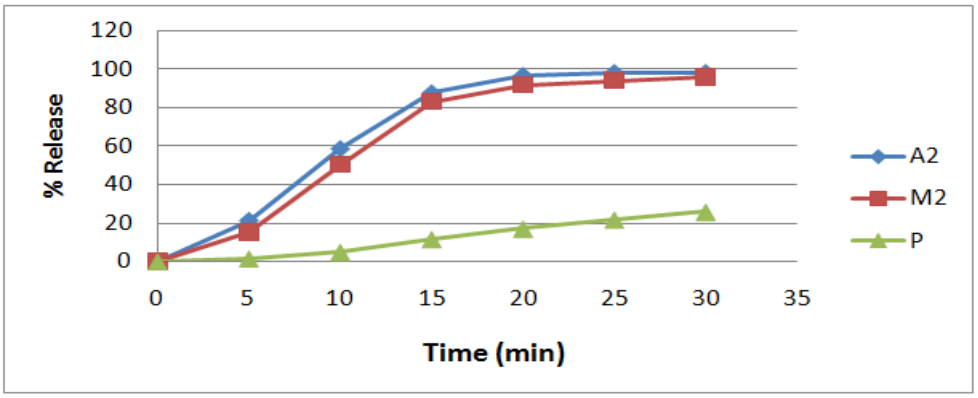

Figure 10 : In vitro dissolution of S-SMEDDS A2, S-SMEDDS M2 and Plain drug

Solid state characterization of solid SMEDDS

FT-IR studies

Figure 13 illustrates the FT-IR spectra of Lamotrigine, Aerosil200, S-SMEDDS-A2 formulation and Physical mixture. The pure drug Lamotrigine exhibit characteristic peaks at 3089 cm^{-1} (C-H aromatic), 1619 cm^{-1} (C=C)stretching, 3450 cm^{-1} (N-H)stretching, 1577 cm^{-1} (C=C aromatic) and peak at 1052 cm^{-1} can be assigned to the ortho distributed C-Cl stretching (Figure 13a). The peaks at 3089, 1619and 1577 cm^{-1} were disappeared and the drop in intensity of peaks at, 3450 and 1052cm^{-1} in S-SMEDDS-A2 formulation indicate physical interaction (Figure 13c). However the absence of extra peaks suggests that there was no possible chemical interaction between the drug and formulation ingredients

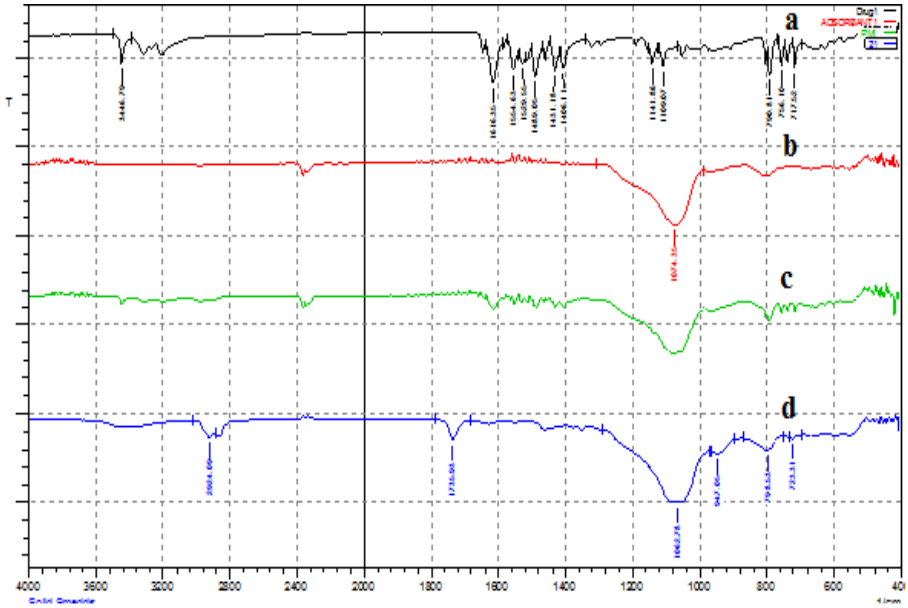

Figure 11: FT-IR spectra of a) Lamotrigine b) Aerosil 200 and c) S-SMEDDS-A2 d) physical mixture

X-ray powder diffraction

The powder X-ray diffractometry patterns are presented in Figure. 14. Lamotrigine had sharp peaks at the diffraction angles, showing a typical crystalline pattern (Figure.14b). Aerosil200 (Figure.14a) showed no intrinsic peaks. All of the major characteristic crystalline peaks for the drug and each carrier were observed in these physical mixtures (Figure.14d). S- SMEDDS-A2 formulation showed peaks at diffraction angles, showing an amorphous pattern (Figure.14c). Thus, like the DSC results, Lamotrigine was present in a changed amorphous state in the SMEDDS formulations prepared with Aerosil 200

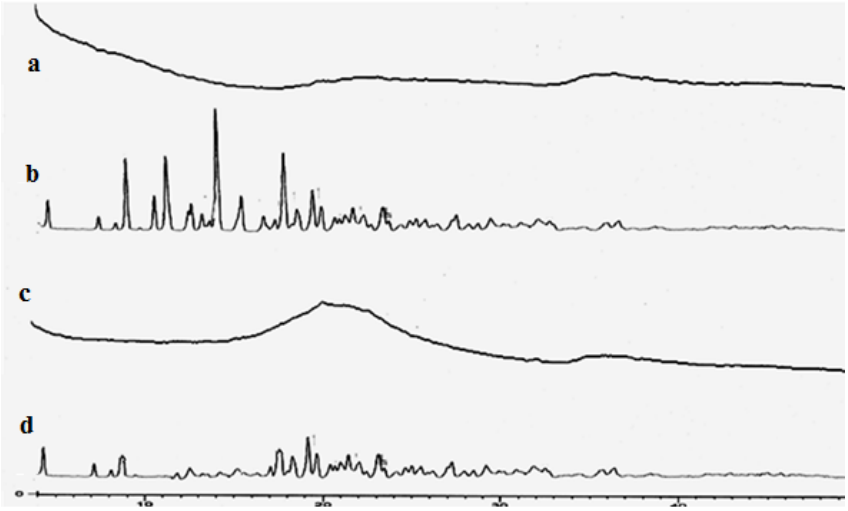

Figure 12 : XRD pattern of a) Aerosil 200 b) Lamotrigine c) S-SMEDDS-A2 d) physical mixture

DSC

DSC curves of pure Lamotrigine, Aerosil 200, S-SMEDDS-A2 and the physical mixture are shown in Figure. 15**.** The physical mixtures were prepared by simply mixing the carriers and drug. Pure Lamotrigine showed a sharp endothermic peak at about 218 ^{0}C corresponding to its melting point and indicating its crystalline nature (Figure 15c). Aerosil200 did not show any peak over the entire range of the tested temperatures (Figure 15a). The melting point, which appeared in the drug peak, was shown with a reduced intensity in physical mixture (Figure 15b) .No obvious peak of the drug was found in the solid SMEDDS–A2 indicating that the drug must be present molecularly dissolved state in solid SMEDDS

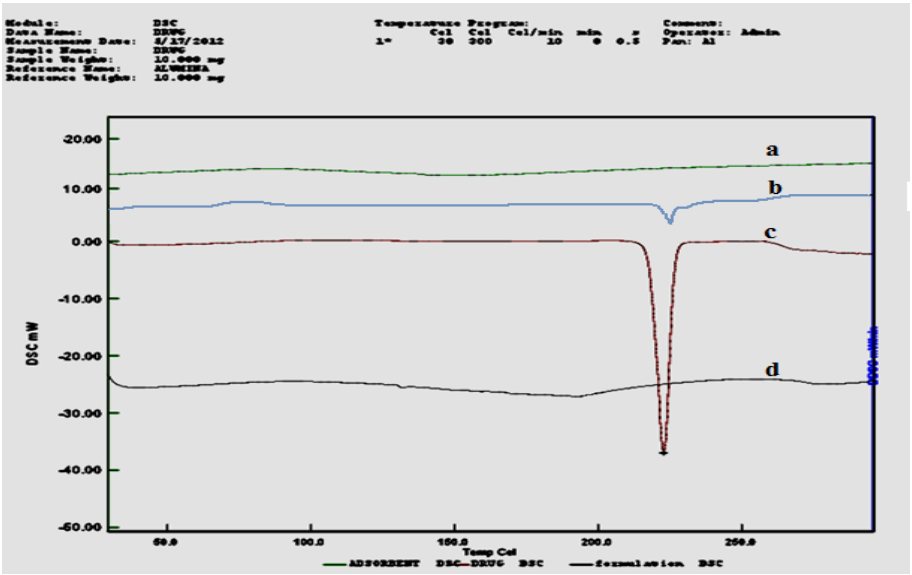

Figure 13: DSC of a) Lamotrigine b) Aerosil 200 c) S-SEDDS-A2 d) physical mixture

Morphological analysis of solid SMEDDS

The scanning electron micrographs of Aerosil 200 and solid SMEDDS are shown in Fig.16. Aerosil 200 (Figure.16a) appeared with a rough surface with porous particles. However, the solid SMEDDS (Fig.16b) appeared as smooth-surfaced Aerosil 200 particles, indicating that the liquid SMEDDS is absorbed or coated inside the pores of Aerosil 200.

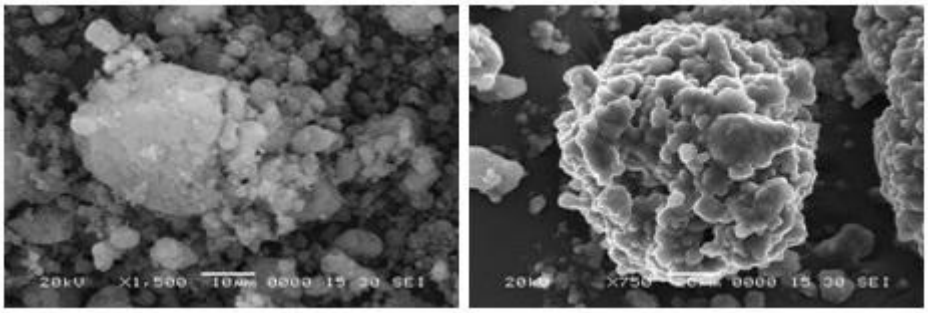

Figure 14: Scanning electron micrographs: (a) Aerosil 200; (b) solid SMEDDS

Table 2: Pharmacokinetic parameters of Lamotrigine in rat plasma following oral administration of S-SMEDDS-A2 and control formulation

Parameters	Control Formulation	S-SMEDDS Formulation (A-2)
Cmax(µg /ml)	1.64±1.35	5.46±1.02
Tmax(h)	1.0±0.0	1.0±0.0
$AUC_{0-\infty}$(µg h ml^{-1})	53.23±1.56	165.15±3.24
F	-	3.10±0.55

(mean, n=4)

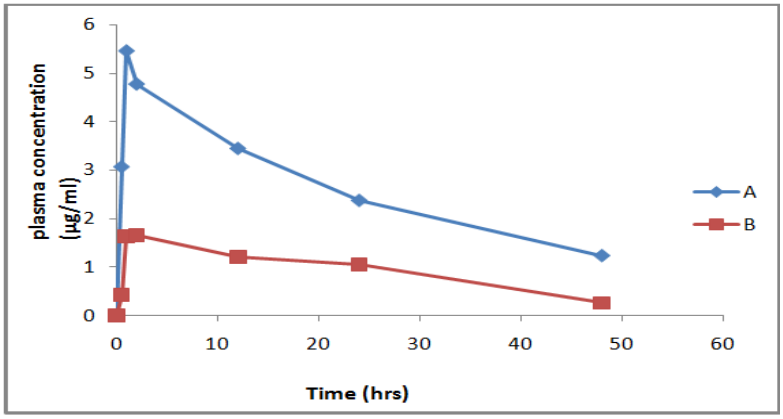

Figure 15: Pharmacokinetic profiles of Lamotrigine from A) S-SMEDDS-A2 and B) Control in rat plasma

***In vivo* studies**

Bioavailability study

In order to derive the conclusions, pharmacokinetic studies in rats were conducted to assess the

feasibility of Lamotrigine loaded S-SMEDDS for improved oral delivery. The mean plasma concentration vs. time profiles of Lamotrigine following per oral administration of S-SMEDDS-A2 formulation in comparison to control was shown in figure. 17 and the pertinent pharmacokinetic parameters were derived (Table 2). It is evident from figure. 17. That Cmax following treatment with S-SMEDDS-A2 formulation was significantly higher compared to control ($p<0.001$). However the time to reach the peak concentration (Tmax) remained constant which clearly indicate that the transformation of emulsion from S-SMEDDS-A2 was spontaneous. The AUC values which indicate the extent of absorption was 165.15±3.24 µg h mL^{-1} following oral administration of S-SEEDS-A2 and was significantly higher compared to control (53.23±1.56 µg h mL^{-1}) ($p<0.001$). The relative bioavailability (F) of Lamotrigine following oral administration of S-SMEDDS-A2 was also significantly higher compared to control ($p<0.001$). Overall, it is apparent from the results that the rate and extent of absorption of Lamotrigine has been markedly improved from S-SMEDDS-A2 compared to control.

CONCLUSION

From the entire study it was concluded that there was an increase in both the solubility and dissolution rate of drug in S-SMEDDS-A2 as compared to dissolution rate of pure Lamotrigine. The significant increase in solubility and dissolution was observed in formulation S-SMEDDS-A2. From the *in vivo* studies it was confirmed that bioavailability of S-SMEDDS-A2 increased significantly compared with pure Lamotrigine.

ACKNOWLEDGEMENT

The authors would like to thank Dr. M.J. Patil, Principal MMM's College of Pharmacy, and Pune for his constant support and encouragement.

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