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Original Research Article

SOLUBILITY ENHANCEMENT OF LAMOTRIGINE USING SOLID SELF EMULSIFIED DRUG DELIVERY SYSTEMS

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ABSTRACT

Lamotrigine is a novel anti epileptic drug which belongs to BCS Class II. Its poor aqueous solubility limits its oral bioavailability. The aim of the current work was to utilize the self emulsifying drug delivery platform to enhance the dissolution of Lamotrigine and thereby improve its oral bioavailability.

The composition of the oil phase and the surfactant and co surfactant mixture (S-mix) was optimized by varying the HLB value of the S mix from low of 6 to a high of 14. The stability of the emulsion was determined by physical observation. The drug loaded s-mix was adsorbed on to a solid carrier and the resultant powder was subjected to in vitro dissolution testing in water and in the compendia media. The results were compared to those of plain drug from equivalent mixture.

Key words: Lamotrigine, BCS class II, oil phase, s-mix, HLB.

INTRODUCTION

Lipid-based formulations are well known approach to enhance water solubility and oral bioavailability particularly, the self-Microemulsifying drug delivery system (SEDDS) [1,2]. SEDDS formulations are isotropic mixtures of an oil, a surfactant, a co surfactant (or co solvents), and a drug. The basic principle of this system is its ability to form fine oil-in-water (o/w) micro emulsion under gentle agitation following dilution by aqueous phases. This spontaneous formation of an emulsion in the GI tract presents the drug in a solubilized form, and the small size of the formed droplet provides a large interfacial surface area for drug absorption[3]. Further, the presence of oily phase in the formulation helps improve bioavailability by affecting the drug absorption.. SEDDS are generally encapsulated either in hard or soft gelatin capsules. Lipid formulations however may interact with the capsule resulting in either brittleness or softness of the shell [4]. To overcome this problem SEDDS need to convert into Solid SEDDS. Numerous reports states that, the major techniques for converting SEDDS to S-SEDDS are spray cooling, spray drying, adsorption onto solid carriers, melt granulation, melt extrusion, super-critical fluid based methods and high pressure homogenization [5-7]. Out of all these processes the physical adsorption process is simple and involves adsorption of the liquid formulation on to solid carriers by physical mixing.

Lamotrigine (Lamictal) is 6-(2,3-Dichlorophenyl)-1,2,4-triazine-3,5-diamine, belonging to anti epileptic agents. Lamotrigine is classified as BCS class II drug, having high permeability and poor water solubility (0.17 mg/mL at 25°C). The poor water solubility of Lamotrigine is responsible for its poor dissolution rate, which ultimately leads to variable absorption of Lamotrigine [8].

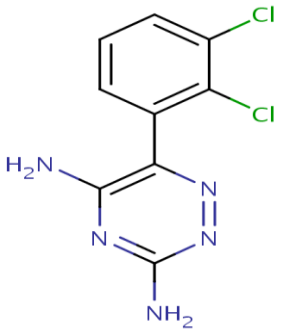

Fig.1.Chemical Structure of Lamotrigine

The main objective of the study was to determine the effect of HLB values of the surfactant-co surfactant mixtures on the aqueous solubility of an oily solution of Lamotrigine. The in vitro dissolution studies were conducted for the S-SEDDS in order to determine how the delivery system functions from a formulated solid dosage form.

MATERIALS AND METHODS

Materials

Lamotrigine USP (gift sample from RA Chem, Hyderabad), Sunflower oil ,Olive oil, Coconut oil, Palm oil, Soya oil(Doubly Refined), Sodium lauryl sulphate (SLS, Merck India), Tween 80 (Merck, India), Span 60 (Merck India), Microcrystalline cellulose (Avicel PH 101, FMC), Colloidal Silicon Dioxide (Aerosil 200 Pharma, Degussa) were used for this study. All other chemicals and reagents were of AR grade from Merck. Purified water USP was used where indicated.

METHODS

DETERMINATION OF SATURATION SOLUBILITY OF LAMOTRIGINE IN DIFFERENT OIL PHASES [9]:

The solubility of Lamotrigine in various oil phases was determined by adding an excess amount of drug in 5 ml of each individual oils contained in stopper vials (15 ml capacity) separately. The dispersion was mixed for 15 minutes using a vortex mixer and the vials were then shaken using orbital shaker at 25°C±1°C for 72 hr to reach equilibrium. The equilibrated samples were removed from the shaker and centrifuged (3000 rpm) for 15 min. The supernatants were taken out and filtered through a membrane. The concentration of Lamotrigine in various phases was determined by UV spectroscopy (Labindia) at their respective λmax 267nm..

EFFECT OF SURFACTANTS ON SOLUBILITY OF LAMOTRIGINE IN SUNFLOWER OIL :

The solubility of Lamotrigine in sunflower oil in presence of various surfactants was determined by adding an excess amount of drug to the dispersion of oil and surfactant solution in 5 ml of each selected individual surfactants contained in stopper vials (15 ml capacity) separately. The mixture was mixed using a vortex mixer and the vials were then shaken using orbital shaker at 25 °C±1 for 72 hr to reach equilibrium. The equilibrated samples were removed from the shaker and centrifuged (3000 rpm) for 15 min. The supernatants were taken out and filtered through a membrane. The concentration of Lamotrigine in various phases was determined by UV spectroscopy (Labindia) at λmax of 267nm .

SELECTION OF SURFACTANT MIXTURES (S-MIX) BASED ON HLB VALUE:

The effect of HLB of S-mix on the formation and stability of oil in water emulsion was evaluated from a low HLB of 6.0 to a high HLB of 14.Two types of surfactant mixtures were evaluated for achieving the targeted HLB range (Table 1)

(1) TWEEN 80 + SPAN 60

(2) SLS + SPAN 60

5 ml of the oil s-mix mixture was dispersed in 20 ml of water in a 50 ml stopered flask and gently shaken for 15 minutes on wrist shaker. The flasks were allowed to stand and the stability of the emulsion was observed for separation at every hour for 8 hours. Observation of no phase separation

at time > 4 hours was considered as significantly stable formulation.

PREPARATION OF DRUG LOADED SEDDS AND CONVERSION TO S-SEDDS [10,11]:

.S-mix mixtures of SLS and Span 60 in the HLB range of 10, 12 and 14 (F8, F9, F10) were dispersed in 4 ml of Sunflower oil. To this 0.5 g of Lamotrigine was added and dispersed using probe Sonicator. Each of the SEDDS of Lamotrigine was adsorbed onto 9:1 ratio of Micro Crystalline Cellulose (Avicel PH 101) and Aerosil200 Pharma by physical mixing in mortar and pestle. The resulting solid SEDDS (S-SEDDS) was triturated for 15 minutes to ensure that the mixture was uniformly distributed. The free flowing powder was passed through sieve No.120 and packed in suitable air tight HDPE containers. The composition of all drug loaded formulations is given in Table 2.

MICROMERITIC PROPERTIES OF S-SEDDS [12,13]

All S-SEDDS were evaluated for micromeritic properties such as angle of repose, bulk and tapped density, Carr's index and Hausner's ratio these properties are listed in Table 3.

No significance difference in any of the physical properties was observed for all S-SEDDS powders.

DRUG CONTENT [14]

The drug content of Lamotrigine in each formulation was estimated by weighing out appropriate quantity of the S-SEDDS equivalent to 25 mg of Lamotrigine in 100ml of Methanol. The volumetric flasks were sonicated for 30 min. This mixture was filtered after making up the volume. An aliquote of the clear filtrate was suitably diluted to give a solution of 10 ug/ml of Lamotrigine.. Absorbance was measured at λ max 267 nm using UV spectrophotometer and compared with that of a standard 10 ug/ml solution in Methanol.

IN VITRO DRUG RELEASE STUDY

Based on the assay values, powder equivalent to 25 mg of Lamotrigine was filled into size '0' empty hard gelatin capsule shells and subjected to in vitro dissolution profile testing by using water as the dissolution medium as well as by using 0.1N HCl as the dissolution testing medium. 0.1N HCl is the compendia medium for Lamotrigine [15]. The dissolution profile testing parameters were set as below:

Apparatus: USP Type I Basket

RPM: 100

Volume: 900 ml

Temperature: 37 ± 0.5°C

Sampling time interval (minutes): 5, 10, 15, 20, 45, 60

Analysis: By UV spectroscopy at 267 nm.

RESULTS

Table.1.HLB SCREENING STUDIES FOR S-MIX FORMULATIONS CHART

TARGET HLB										
INGREDIENTS	F 1	F2	F3	F4	F5	F6	F7	F8	F9	F10
SPAN60%w/w	88	70	53	35	17	95	87	80	72	64
TWEEN80 %w/w	12	30	47	65	83	-	-	-	-	-
SLS(%w/w)	-	-	-	-	-	5	13	20	28	36
OIL(ml)	4	4	4	4	4	4	4	4	4	4
WATER(ml)	20	20	20	20	20	20	20	20	20	20

Table.2.Formulation of Drug Loaded Preparation

Ingredients	**F0**	**F11**	**F12**	**F13**
Lamotrigine	0.5g	0.5g	0.5g	0.5g
Sunflower oil	-------	4ml	4ml	4ml
SLS(%w/w)	-------	20	28	36
SPAN60(%w/w)	-------	80	72	64
MCC(g)	9	9	9	9
AEROSIL(g)	1	1	1	1

Table.3.Micromeritic properties and drug content of S-SEDDS

Properties	F11	F12	F13
ABD	0.25	0.26	0.23
TBD	0.33	0.32	0.35
Carr's Index	24.2	21.87	34.2
Hausnaer's ratio	1.32	1.28	1.52
Angle of repose	27.4	24.65	25.63
Drug content/assay (%w/w)	90.27	92.56	93.74

Table.4.HLB Screening Studies

Formulation No	HLB	Time for Stability
F1	6	<2hrs
F2	8	<2hrs
F3	10	<3hrs
F4	12	<4hrs
F5	14	>4hrs
F6	6	<2hrs
F7	8	<2hrs
F8	10	>4hrs

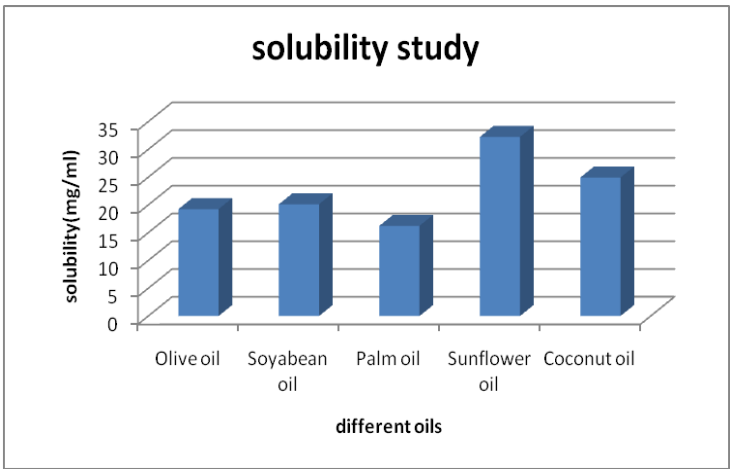

Fig.2.Saturation solubility of Lamotrigine in different oils

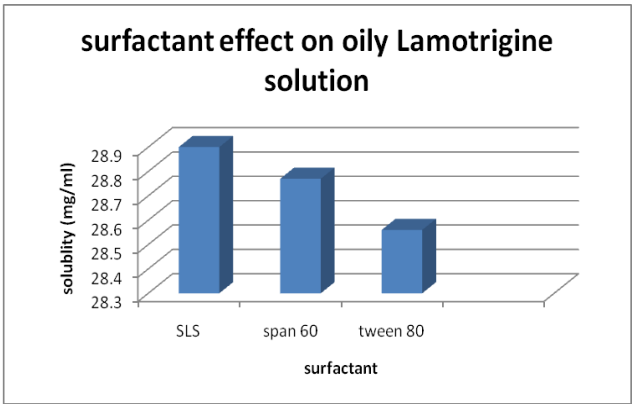

Fig.3.Effect of surfactants on oily Lamotrigine solution

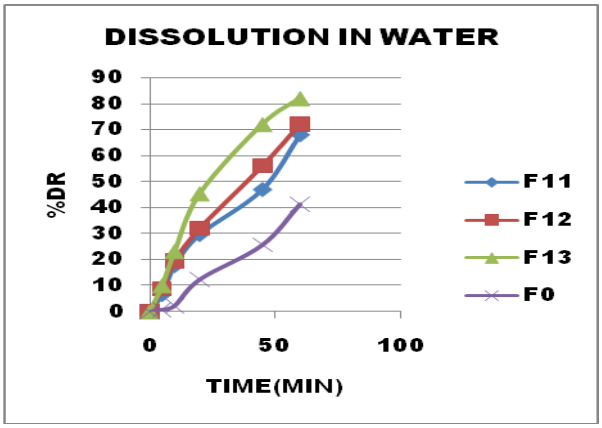

Fig.4.Dissolution in water

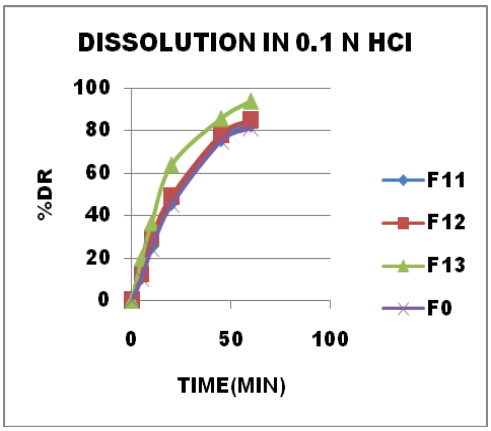

Fig.5.Dissolution in 0.1 N HCl

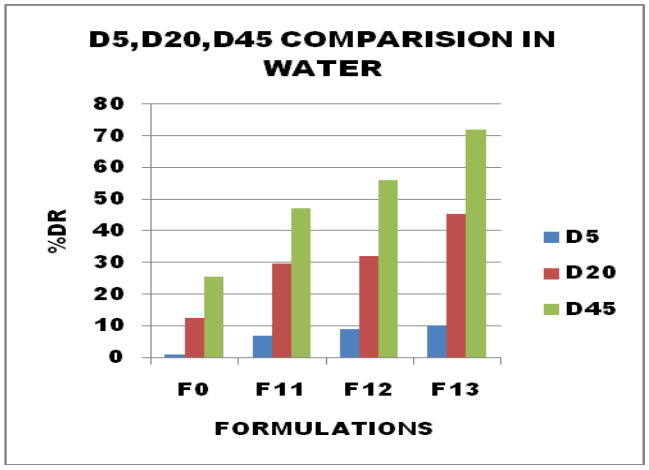

Fig.6.D5,D20,D45 comprision in water

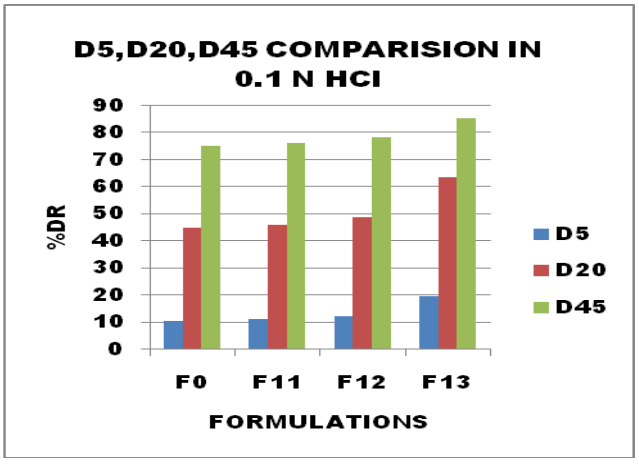

Fig.7.D5,D20,D45 comparision in 0.1 N HCl

DISCUSSION

EQUILIBRIUM SOLUBILITY OF LAMOTRIGINE IN DIFFERENT OILS

The equilibrium solubility of Lamotrigine in various oils is shown in Fig 2. The data indicates that Sunflower oil has the maximum solubilization capacity for the drug.

EFFECT OF SURFACTANTS ON THE EQUILIBRIUM SOLUBILITY OF LAMOTRIGINE IN SUNFLOWER OIL

The solubility values in presence of different surfactants are shown in Fig 3. None of the three surfactants significantly affect the solubility of Lamotrigine in sunflower oil

HLB SCREENING STUDIES FOR SELECTION OF S-MIX COMPOSITION

The stability of the oil water emulsion in presence of different HLB values of the surfactant mixtures (S-mix) is recorded in Table 4. Formulation F8, F9 and F10 exhibit emulsion stability for > 4 hours. This indicates that S-mix of SLS and Span 60 in the HLB range of 10, 12 and 14 give the best emulsion stability

IN VITRO DRUG RELEASE FOR DRUG LOADED S-SEDDS:

The effective delivery of a drug from S-SEDDS is proposed to be governed primarily by small particle size and the polarity of the resulting oil droplets, which permits a faster rate of drug release into the aqueous phase. The solubilized drug may not precipitate in the lumen, and undergo rapid absorption which is independent of the lipid digestion process.

In vitro studies were performed to compare the enhancement of solubility of Lamotrigine in S-SEDDS with that of plain drug in dissolution media water (Fig 4) and 0.1 N HCl (Fig 5)

Dissolution at 5min (D5), 20min (D20), 45min(D45) were compared in both the dissolution media.

COMPARISION OF D5,D20,D45 MIN :

1. Dissolution for all three HLB values are significanlty greater than plain drug (F0) in water.
2. The dissolution rate and extent is significantly greater in formulation F13 whose HLB is 14 (Fig 5).
3. This indicates that the HLB of the formulation plays a significant role in enhancing the solubility of the practically insoluble Lamotrigine.
4. All formulations achieve >75% release in 45 minutes in 0.1 N HCl which is the sink condition (Fig 6).
5. However, the rate and final extent of dissolution depends on the HLB of S-SEDDS.
6. HLB 14 (F13) is significantly faster and more complete even in the less challenging dissolution medium.
7. It could be suggested that S-SEDDS resulted in spontaneous formation of emulsion with smaller droplet size, which permitted a faster rate of drug release into the dissolution medium as compared to plain Lamotrigine .

CONCLUSION

From study it was concluded that, S-SEDDS provides an attractive and easy alternative to improve the solubility of the practically insoluble Lamotrigine. The type of surfactant selected and the HLB of the surfactant mix used along with the oil seems to be critical in developing a successful S-SEDDS fomulation. For Lamotrigine, Sunflower oil and combination of SLS and Span 60 used at an HLB of 14 gave a product which gives faster and significanly compelte dissolution for the drug from the S-SEDDS formulation.

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