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Formulation and Evaluation of Self Microemulsifying Drug Delivery System (SMEDDS) of Sertraline HCl

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Abstract

Aim: The present work aimed at formulating a self micro emulsifying drug delivery system (SMEDDS) for sertraline HCl.

Objective: The objective of the present study was to enhance the water solubility of poorly-water soluble drug sertraline HCl by forming liquid SMEDDS. Sertraline HCl is an antidepressant agent belongs to BCS class-2 category having poor solubility and permeability.

Experimental: Solubility study of sertraline HCl carried out in various excipients. Based on solubility study, oleic acid as a oil, tween 80 as surfactant and PEG 400 as co-surfactant were selected a component of liquid SMEDDS formulation. Then water titration was done to know phase behaviour to identify microemulsion zone. The prepared system was characterized for self emulsification time, % transmittance, droplet size and thermodynamic stability study. Result of dissolution rate of sertraline HCl SMEDDS were compared with those of pure drug. *In-vitro* dissolution study indicates high dissolution rate of liquid SMEDDS over the pure drug. Thus SMEDDS formulation helps to improve the solubility.

Keywords: SMEDDS, Sertraline HCl, Solubility enhancement, *in-vitro* dissolution

1. INTRODUCTION

Self micro-emulsifying drug delivery system (SMEDDS) is an isotropic blend of oils, surfactants and co-surfactant that forms microemulsion, upon mild agitation followed by dilutions in aqueous media, such as gastrointestinal (GI) fluids [1]. SMEDDS represents the systems forming transparent microemulsions with oil droplets ranging between 100 and 250 nm [2]. In SMEDDS drug remains in a dissolved state, in small droplets of oils during its transit throughout gastrointestinal tract [3]. Upon oral administration and dispersion in gastric fluids, the microemulsion formation is facilitated by the gentle agitation of the gastrointestinal tract (GIT). Ideally, the selected surfactant-oil mixtures maintain their drug solubilization capacity upon dispersion to avoid SMEDDS has been reported as excellent alternatives for the enhancement of solubility of drugs having poor aqueous solubility. In SMEDDS drug remains in precipitation until the drug can be absorbed from the GIT [4].

Sertraline HCl, (1S,4S)-4-(3,4-*di* chlorophenyl)-1,2,3,4-tetrahydro-N-methyl-1-naphthaleneamine, hydrochloride (Fig. 1) is a serotonin-specific reuptake inhibitor that is effective in treating several disorders such as major depression, obsessive-compulsive disorder, panic disorder, and social phobia. Sertraline HCl belongs to class II drugs (drugs having low water solubility and high permeability) according to the Biopharmaceutical Classification System (BCS) [5]. Its solubility in water ranges between 3.2 and 3.6 mg/mL at room temperature. The rate-limiting step in the bioavailability of class II drugs is most likely the low solubility/poor dissolution rather than the permeability. Hence, there is a correlation between in vitro dissolution and the in vivo bioavailability [6]. Sertraline HCl is a weak base with a pKa of 9.48. Its solubility is pH-dependent and the highest solubility is attained at pH 4.5. Sertraline HCl is slowly absorbed when administered orally. It exhibits linear dose-proportional pharmacokinetics over a range of a single dose of 50 to 200 mg and undergoes extensive first-pass metabolism. Thus, the main two problems regarding sertraline HCl are the low solubility/poor dissolution which is pH-dependent and the extensive first-pass metabolism. These problems resulted in the low oral bioavailability of the drug (44%). Several strategies were used to enhance the dissolution rate of poorly soluble drugs.

The objective of the present study was to develop a SMEDDS of sertraline HCl to improve its solubility. Solubility study of sertraline HCl was carried out in various vehicles and based on solubility data SMEDDS formulations were prepared by using oleic acid (oil), Tween 80 (surfactant), and PEG 400 (co-surfactant). Prepared SMEDDS formulations were evaluated for emulsification time, cloud point, globule size, zeta potential and drug content.

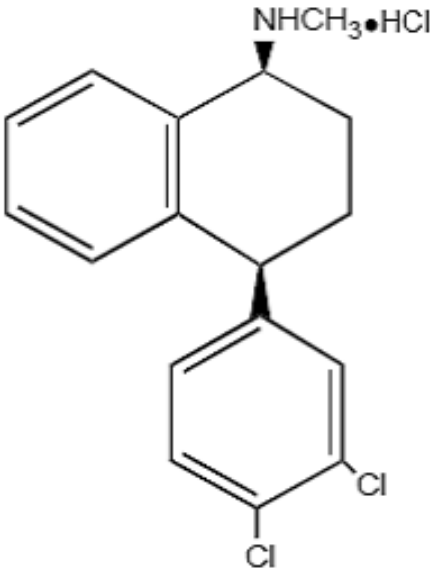

Fig 1: Structure of Sertraline HCl

2. MATERIAL AND METHOD

2.1 Material

Sertraline HCl was received as a gift sample from Wockhardt Ltd., .Aurangabad, India. Tween 80, Oleic acid and PEG 400 was received from Research-lab Fine Chem. Industries, Mumbai, India. All the chemicals and reagents used were of AR grade.

2.2 Solubility study

Solubility studies were carried by placing an excess amount of sertraline HCl in a screw capped vials containing 2 mL of vehicles (oils, surfactants and co surfactants) as shown in Table 1. The suspensions of vehicles were heated on a water bath at 40 °C to facilitate the solubilization using vortex mixer. The suspensions were then continuously agitated on a rotary shaker for 48h at ambient temperature. After reaching equilibrium the samples were centrifuged at 5000 rpm for 15 min and the supernatant was taken, filtered through 0.45 µm membrane filters. The filtrates were suitably diluted with methanol and analyzed spectrophotometrically for the dissolved drug at 273 nm. Blank was prepared by dissolving respective vehicles in methanol with same dilution as for the samples. The experiment was performed in triplicate and results were represented as mean value (mg/mL) ± SD [5].

2.3 Construction of pseudo ternary phase diagram

Based on the solubility data, Oil (Oleic acid), Surfactant (Tween 80) and co-surfactant (PEG 400) were selected for construction of pseudo ternary phase diagrams. To determine maximum microemulsion existence area of SMEDDS formulation, water titration method was used. Mixtures of surfactant and co-surfactant (S/Cos) containing two different ratios (1:1, 2:1) were prepared. The oil and S/Cos were taken in ratios from 1:1 to 1:9 with a total mass of 1 g. The mixtures were vortexed and titrated with water using a micro syringe under gentle agitation, then observed visually for turbidity or clarity. Phase diagrams were constructed for identifying the emulsification region. All studies were repeated thrice. Pseudo ternary phase diagrams were constructed by using CHEMIX school software v [6].

2.4 Preparation of SMEDDS

The SMEDDS were prepared by dissolving a single dose of sertraline HCl (25 mg) in oleic acid (Oil) placed in a glass vial at ambient temperature by stirring on a vortex mixer. Later to the above prepared solution, Tween 80l (surfactant) was added followed by addition of PEG400 (co-surfactant). The resultant mixtures were vortexed for 20 min to obtain a homogenous transparent preparation. The compositions of SMEDDS formulations of sertraline HCl with varying ratios of oil, surfactant and co-surfactant are shown in Table 2. A 1:1 ratio of S/Cos mix was chosen for formulation. The prepared SMEDDS formulation was stored at RT until used [7].

2.5. Characterization of SMEDDS

2.5.1. Visual Assessment of Self- Emulsification

In this method, a unit dose of the formulation was introduced into 250 mL of water in a glass beaker that was maintained at 37 ± 0.5 ºC and the contents mixed gently using a magnetic stirrer. The tendency to emulsify spontaneously and the time taken for the emulsion formation were assessed visually [8].

2.5.2. Drug Content

Liquid SMEDDS containing sertraline HCl, each equivalent to 25 mg was dispersed in suitable quantity of methanol. The samples were mixed thoroughly to dissolve the drug in methanol, centrifuged at 3000 rpm for 15 min using 12 C micro-centrifuge (Remi Motors, Mumbai, India) to separate the undissolved excipients. The supernatant was suitably diluted and analyzed spectrophotometrically at 273 nm using Schimadzu 1700 UV visible spectrophotometer (Schimadzu Corporation Kyto, Japan) [9].

2.5.3. % Transmittance

The SMEDDS were reconstituted with distilled water and the resulting micro emulsions were observed visually for any turbidity. Thereafter its % transmittance was measured at 650 nm using UV visible spectrophotometer (SHIMADZU UV-1700) against distilled water as the blank. The studies were conducted after 100 times dilution [10].

2.5.4. Cloud point and thermodynamic stability

Cloud point determinations were carried out within the temperature range 40 to 60 ºC. The stable formulation shows cloudiness above 60 ºC. Prepared sertraline HCl SMEDDS formulations were diluted by distilled water in a ratio of 1:100. The diluted samples were placed in a water bath initially at 25 °C and increased the temperature gradually. Recorded the temperature at which cloudiness occurred in a formulation. Thermodynamic stability study was designed to identify and avoid the metastable SMEDDS formulations. For evaluating the thermodynamic stability, the formulations were subjected to heating-cooling cycle (4°C and 45°C) and freeze-thaw cycle (−21°C and +25°C) with storage at each temperature of not less than 48 h. For centrifugation stress, the formulations were centrifuged at 3500 rpm for 15 min, and the extent of phase separation was monitored [11].

2.5.5. Determination Droplet size and zeta potential

Prepared sertraline HCl SMEDDS formulations (1 mL) were diluted to 100 mL with deionized water with constant stirring for 5 min on a magnetic stirrer. The resultant mixtures were subjected to determine particle size, by using particle size analyzer and zeta potential by using zeta sizer (Malvern Instrument, UK) [12,13].

2.5.6. In vitro drug release studies of SMEDDS

In vitro drug release studies were performed using a modified dialysis technique. Initially, the dialysis tubing was soaked in the dialysis medium for 12 h at room temperature which was treated at 40 °C before the start of the experiment. The diluted SMEDDS formulation (equivalent to 10 mg of sertraline HCl) was placed in dialysis tubing (Hi Media Membrane, Mumbai, cut off 12000-14000 Da) and clamped on both sides. The secured dialysis tube was allowed to rotate freely in the dissolution vessel of USP XXIV Type-II dissolution apparatus (Electrolab TDT-06 T, Mumbai, India) containing 500 mL of 0.1N HCl dialysis medium at 37°C ± 0.5 °C and stirred at 50 rpm. An aliquot of 5 mL was withdrawn at predetermined time intervals and filtered through 0.45 µm

filter. The withdrawn volume was replenished immediately with the same volume of fresh medium to keep total volume constant and maintain sink conditions. The concentration of sertraline HCl in the filtrate was analyzed using the UV spectrophotometer at 273 nm [14,15].

3. Results And Discussion

3.1. Solubility studies

Solubility of sertraline HCl was determined and is given in Table 1. The oil represents one of the most important excipients in the SMEDDS formulation because it can solubilize marked amount of the lipophilic drug and facilitate self emulsification. Thus, drug should be sufficiently solubilized in the oil to be emulsified. It is observed that, drug was highly soluble in oleic acid as comparative to other synthetic oils. Thus Oleic acid was selected as the oil phase for further study. Drug was also highly soluble in Tween 80 as compared to other surfactants used. It is observed that, drug was highly soluble in PEG 400 as compared to other co-surfactants used.

Table 1. Solubility of sertraline HCl in different vehicles

Sr.No	Ingredient	Solubility (mg/mL)
1	Water	3.7
2	Tween 80	78.39
3	Span 80	30.16
4	PEG 400	65.16
5	PEG 200	51.00
6	Transcutol	40.39
7	Oleic acid	45.23
8	Olive oil	9.25
9	Castor oil	15.43

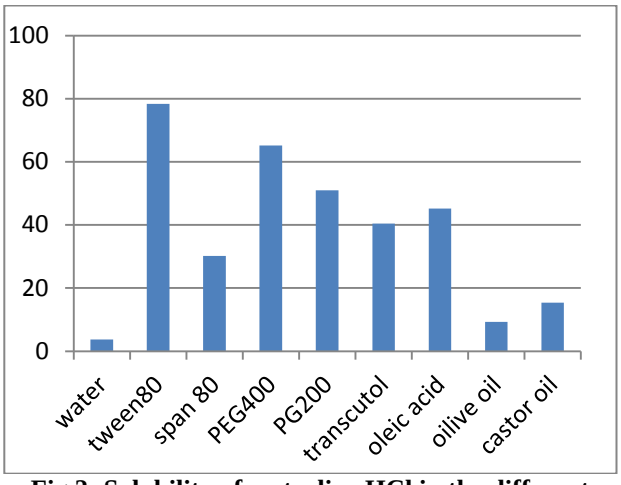

Fig 2: Solubility of sertraline HCl in the different vehicles

3.2. Construction of pseudo ternary phase diagram

A series of SMEDDS were prepared and their self-emulsifying properties were observed visually. It has been reported that the drug incorporated in SMEDDS system might have some effect on the self-emulsifying capacity. The translucent and low viscosity microemulsion areas are illustrated in Fig. 2. The pseudo-ternary phase diagrams were constructed by varying the concentration ratio with oil and surfactant in 1:1 (A), 2:1 (B), and 3:1 (C) ratios. The black dots area represents o/w microemulsion existence ranges. Higher concentrations of co-surfactant correlated with increased space for self emulsifying in phase diagrams. The opaque or precipitation status was observed, in case a self-emulsifying droplet formed from the ratio of surfactant (S)/co-surfactant (Cos) [1:1 and 2:1 (v/v)]. The ratio of S/Cos = 1:1 was selected because all kinds of surfactants are potentially irritating or poorly tolerated; for example, large amounts of surfactants may cause gastrointestinal tract irritation

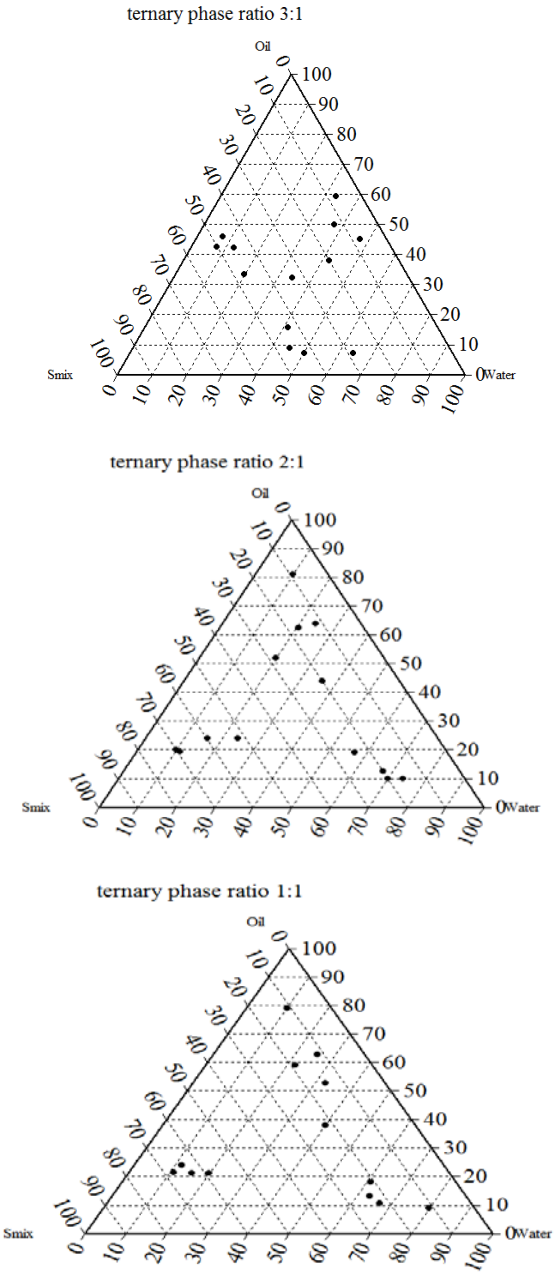

Fig 3. Ternary phase diagrams of systems at room temperature and 37 °C (dotted areas indicate microemulsion regions, one phase system)

3.4 Characterization and Preparation of SMEDDS

9 batches of liquid SMEDDS were prepared as per the composition depicted in Table 2 which was then characterized for various parameters as shown in the same Table 3,4 and 5.

3.4.1. Cloud point, Transmittance and Drug content

The cloud point is the temperature above which the clarity of the formulation turns to cloudiness. This may happen due to phase separation in microemulsion or due to precipitation of the drug. Thus, the stability of the formulation will get affected as well as the absorption of the drug depending on the cloud point. To avoid this phenomenon, the cloud point for SMEDDS should be above body temperature (37°C). In the present case, the cloud point temperatures of select formulations determined were in the range of 48-61ºC (Table 3). This indicates that the formulated SMEDDS will be able to form stable microemulsions in a biological environment without any risk of precipitation of the drug. Higher cloud point also infers stability of the formulation during its shelf life (Table 3). Transmittance of the Sertraline HCl SMEDDS gives idea about the formulation clarity and also the phase separation was easily noticed by clarity and transparency of formulation. The drug content of k1 formulation was found to be 98.95% while other formulation drug content found less than 95% so it was concluded the batch K1 formulation have more drug content as compared to others.

3.4.2 Visual assessment of self emulsification

The efficiency of self-emulsification could be estimated primarily by determining the rate of emulsification which is an important index for the assessment should disperse completely and quickly when subjected to aqueous dilution under mild agitation. The emulsification time of these formulations was in the range of 0 to 2 min.

3.4.3 Thermodynamic stability study

Thermodynamic stability indicates the kinetic stability of formulation and is employed to study the chemical reaction between the excipient of a formulation. The Table 5 shows the screening of thermodynamic stability studies the K1-K9 formulations which are observed for the three evaluation parameter these are the freezes throw cycle, heating cooling cycle and centrifugation. The observation revealed that emulsion could withstand wide range of temperature changes and centrifugal stress without any phase separation and drug precipitation.

Table 2. Composition of SMEDDS formulation of Sertraline HCl

Batch	Ratio (S/Cos)	Oil/S mix Ratio	Drug (mg)	Oil(%)	S/Cos mix (%)	Water (%)
K1		1:4	25	15.29	52.79	32.50
K2	1:1	1:5	25	13.12	63.29	24.05
K3		1:6	25	11.63	62.82	25.53
K4		1:4	25	16.23	62.49	20.63
K5	2:1	1:5	25	12.51	67.56	19.56
K6		1:6	25	11.17	63.82	24.47
K7		1:5	25	9.0	45.04	45.94
K8	3:1	1:6	25	7.51	45.11	47.36
K9		1:7	25	7.19	50.35	42.44

Table 3.Cloud point, % Transmittance,% Drug content

Batch	Cloud point ºC	Transmittance (%)	Drug content (%)
K1	61	91.21	98.23
K2	38	98.12	96.23
K3	42	76.82	81.41
K4	39	81.35	82.35
K5	36	85.36	75.35
K6	37	92.58	81.86
K7	51	91.92	84.52
K8	40	79.95	76.42
K9	48	90.60	75.36

Table 4.self-emulsification assessment of SMEDDS formulation

Formulation	Emulsifying time	Clarity	Stability
K1	1.32	Transparent	Stable
K2	1.20	Transparent	Stable
K3	1.40	Transparent	Stable
K4	1.38	Milky white	Unstable
K5	1.41	Transparent	Stable
K6	1.31	Transparent	Stable
K7	2.1	Milky white	Unstable
K8	2.13	Transparent	Stable
K9	2.10	Transparent	Stable

Table 5.Thermodynamic stability of SMEDDS

Formulation	Centrifugation	Freez thaw cycle	Precipitation	
			After 1 h	After 6 h
K1	No phase separation	No phase separation	Clear	Clear
K2	No phase separation	No phase separation	Clear	Clear
K3	No phase separation	No phase separation	Clear	Clear
K4	No phase separation	No phase separation	Clear	Clear
K5	No phase separation	No phase separation	Clear	Clear
K6	No phase separation	No phase separation	Clear	Precipitation
K7	No phase separation	No phase separation	Clear	Precipitation
K8	No phase separation	No phase separation	Clear	Clear
K9	No phase separation	No phase separation	Clear	Clear

3.4.4 Zeta potential

SMEDDS K1 batch reports positive zeta potential value -12.4 mV as shown in Fig.3. The surfactant (Tween 80) and cosurfactant (PEG 400) used in this study are non ionic which do not contribute any charge to the microemulsion particle.

3.4.5 Droplet size

The droplet size of the emulsion is a crucial factor in self-emulsification performance because it determines the rate and extent of drug release as well as absorption. Smaller droplet size presents a large surface area for drug absorption. hence the optimized sertraline HCl K1 batch showed particle size of 128.6 nm with PDI 0.431.

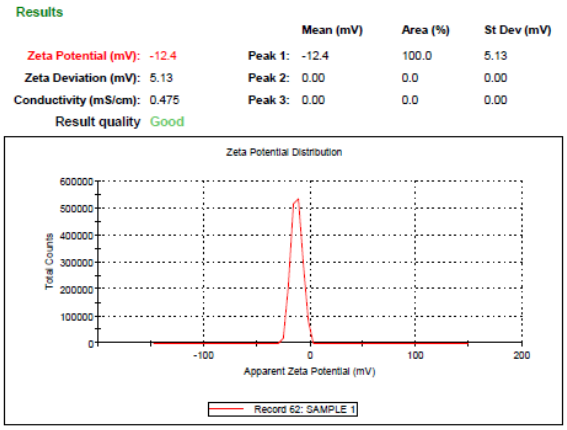

Fig 4. Graph of zeta potential K1 SMEDDs formulation

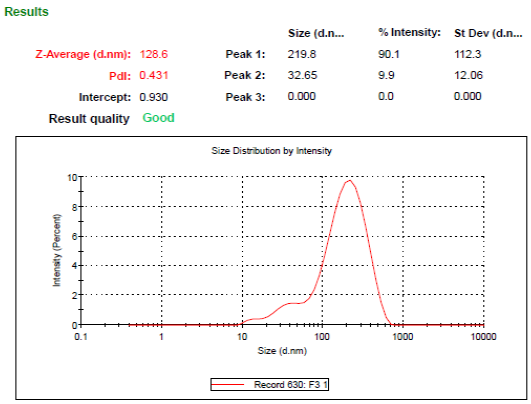

Fig 4: Droplet size distribution of optimized liquid SMEDDS, K1 Batch

3.4.6 In vitro drug release study

Dissolution profile of pure drug, and liquid SMEDDS carried out under standard condition in 0.1N HCl. The drug dissolution studies portrayed optimised liquid SMEDDS formulation exhibited faster drug dissolution, 96.25% within 90 min *vis-a-vis* the pure drug showed maximum drug dissolution up to 15.84% in 90 min respectively. The dissolution of drug was significantly higher from liquid SMEDDS formulation as compared to pure drug.

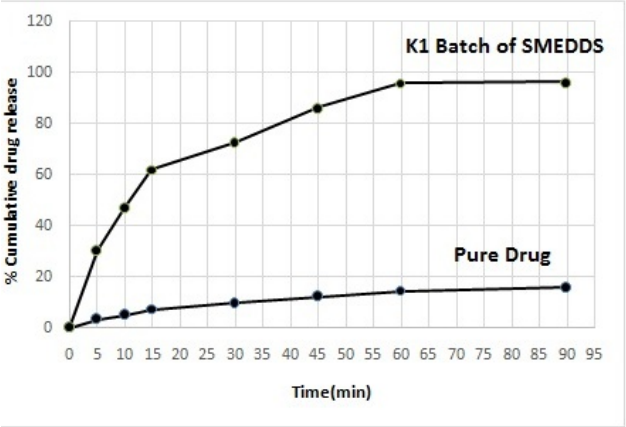

Fig 5: In-vitro Drug release profile of Pure drug, and liquid SMEDDS

4 CONCLUSION

In the current investigation SMEDDS of Sertraline HCl was prepared and evaluated for various parameters. In the current study we described the development of sertraline HCl SMEDDS by means of water titration method. The main objective of this study was to enhance the aqueous solubility of sertraline HCl. The plane drug was used for comparison with SMEDDS. The formulation showed better results in terms of drug content, Self emulsification time, cloud point measurements, % transmittance, zeta potential, SMEDDS, which have been shown to substantially improve oral bioavailability.

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