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Original Article

SELF-NANOEMULSIFYING DRUG DELIVERY SYSTEM FOR SERTRALINE HYDROCHLORIDE: DESIGN, PREPARATION AND CHARACTERIZATION

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ABSTRACT

Objective: Development and characterization of self-nanoemulsifying drug delivery system for sertraline hydrochloride (SNEDDS).

Methods: Solubility of sertraline hydrochloride in various vehicles were determined, and ternary phase diagrams were constructed using a suitable oil, surfactant and cosurfactant system to find out the most efficient self emulsification system.

Results: Capmul® and Lauroglycol® were selected as an oil phase, Tween 80 and Cremophor® as surfactant and Transcutol® as cosurfactant due to their high solublization effect. Various formulations were prepared by simple mixing followed by vortexing. The systems were assessed for droplet size, light absorbance, drug release and emulsification effect. Optimized SNEDDS compositions of oil to surfactant/cosurfactant content did not show phase separation in 0.1N HCl and water, with droplet size varying from 21 nm to 153 nm, which indicates the formation of homogeneous stable nano emulsion in both media. *In vitro* dissolution data showed surprisingly significant enhancement of dissolution rate of sertraline HCl in form of SNEDDS compared to the drug per se.

Conclusion: These results confirm the potentiality of SNEDDS formulation to improve sertraline HClsolubilization and *In vitro* release.

Keywords: Self-nanoemulsifying drug delivery systems (SNEDDS), Sertraline HCl, Surfactant, Cosurfactant.

INTRODUCTION

Sertraline HCl – a selective serotonin re-uptake inhibitor (SSRI) – is indicated for the treatment of depression and anxiety disorders, including obsessive-compulsive disorder, panic disorder and post-traumatic stress disorder. It is considered suitable for the treatment of depressive symptoms in elderly patients, including those with Alzheimer's disease (AD), as it has minimal anticholinergic activity and is essentially devoid of cardiovascular effects[1]. Furthermore, sertraline HCl may be useful in the management of other behavioural problems experienced by AD patients that are likely mediated by the serotonergic system, such as anxiety, irritability and aggression[2].

Sertraline is administered orally in a daily dose of 50 mg. But various problems are associated with its oral delivery such as extensive first-pass metabolism, gastrointestinal disturbances such as nausea, dry mouth, diarrhea, decreased appetite etc., and ultimately its poor bioavailability (40–45%), which required this drug to be taken in high doses in order to maintain adequate plasma levels[3]. Sertraline hydrochloride is practically insoluble in water. Its bioavailability is expected to be limited by its dissolution rate. To overcome these problems, various formulation strategies are exploited including the use of surfactants, lipids, permeation enhancers, micronisation, salt formation, cyclodextrin complexation, nanoparticles and solid dispersions[4].

Oral-based drug delivery system is the most common way to deliver drugs into the blood stream. The water-soluble drugs can diffuse freely and easily in gastrointestinal tract and they have a high bioavailability. However, more and more drugs being discovered nowadays with the advances in biotechnology and pharmaceutical technology are oil-soluble[5]. One way to deliver oil-soluble drugs is to incorporate the drug into an inert lipid vehicle, such as nanoemulsions, oils[6], surfactant dispersions[7] and liposomes[8]. Nano emulsions are isotropic, thermodynamically stable systems and the droplets of nano emulsions are of very small size. Self-nanoemulsifying drug delivery system (SNEDDS) is a pre-mixture of drug, oil, surfactant and cosurfactant that can be used to deliver oil-based drugs. Upon gentle shaking and gastric juice dilution in stomach, it can form nanoemulison spontaneously [9]. The current study was aimed at developing and characterizing SNEDDS for sertraline HCl so as to improve dissolution rate-limited absorption of the drug.

MATERIALS AND METHODS

Materials

Sertraline hydrochloride was kindly donated by Hipharma pharmaceuticals, Egypt. Transcutol® P (2-(2- ethoxyethoxy) ethanol), Capryol® 90 (Propylene glycol monocaprylate), Labrafil® M 2125 CS (Linoleoyl polyoxyl-6 glycerides) and Lauroglycol® 90 (propylene glycol monolaurate; PGML) were kindly supplied by Gattefossé, France. Captex® 355 EP/NF (triglycerides of caprylic/capric acid; Captex®) and Capmul® MCM EP (glycerol monocaprylocaprate; Capmul®) were gifted by ABITEC Corporation, USA. Tween 80® (polyoxyethylenesorbitan mono oleate) was purchased from Oxford Laboratory Reagent, India. Cremophor® ELP (PEG-35 Castor oil; Cremophor®) was kindly donated by BASF, Germany.

Methods

Solubility study

The solubility of sertraline HCl in various oils, surfactants and cosurfactants was determined by adding an excess amount of drug to 2 ml of selected vehicles separately in 5 ml stoppered vials, and mixed using a vortex mixer. The vials were then kept at 25 ± 1.0 ^{0}C in an isothermal shaker for 72 h to attain equilibrium. The equilibrated samples were removed from the shaker and centrifuged at 3,000 rpm for 15 min. The supernatant was taken and filtered through a 0.45 µm membrane filter. The concentration of sertraline HCl was determined spectrophotometrically at 273.4 nm.

Construction of ternary phase diagram

One of the most important characteristics of SNEDDS is the change that occurs when the system is diluted (since it will be diluted by body fluids after administration), which may cause drug

precipitation due to the loss of solvent capacity [10]. Therefore, the phase behavior of each SNEDDS needs to be carefully studied using the phase diagram as a guide. On the basis of the solubility studies of drug, Capmul®, PGML® and Captex® were selected as oil phase. Tween 80 and Cremophore EL® were used as surfactants and Transcutol P® was used as cosurfactant. Oil, surfactant and cosurfactant were grouped in different combination for phase studies [11]. Surfactants and cosurfactant (Smix) were mixed in different ratios (1:1, 2:1, 3:1 and 4:1). Mixture of oil and Smix was prepared at ratios (w/w) of 10:0, 9:1, 8:2, 7:3, 6:4, 5:5, 4:6, 3:7; 2:8, 1:9 and 0:10 in vials. A visual observation was made immediately for spontaneity of emulsification, clarity, phase separation and precipitation of drug and excipients [12]. An aliquot (0.2 ml) of the formulation was introduced into 300 ml of double distilled water in a glass beaker at 37 °C, and the contents were mixed gently with a magnetic stirrer at 100 rpm. The resultant emulsions were stored for 48 h at ambient temperature and observed for clarity, phase separation, drug precipitation and coalescence of droplets. Emulsions showing phase separation, cracking or coalescence of oil droplets were judged as unstable emulsions. All the studies were repeated thrice with and without drug with similar observations made between repeats. Phase diagram was constructed identifying self emulsifying region using Triplot v1-4 software.

Preparation of SNEDDS of sertraline HCl

A series of SNEDDS formulations were prepared using oil, surfactant and cosurfactant. In all the formulations, the amount of sertraline HCl was kept constant (i. e. 25 mg). The amount of SNEDDS should be such that it would solubilize the drug (single dose) completely. Sertraline HCl (25 mg) was added to the mixture, then the components were mixed by gentle stirring and vortex mixing, and heated at 37̊C. The mixture was stored at room temperature until used. So prepared SNEDDS were the concentration of oil, surfactant, cosurfactant and drug [13].

Characterization of SNEDDS

Thermodynamic stability test

To overcome the problem of a metastable formulation, thermodynamic stability tests were performed. Selected formulations were subjected to heating / cooling cycles. Six cycles between the refrigerator temperature (0 ^{0}C) and 40 ^{0}C were performed with storage at each temperature for not less than 48 h. Those formulations, which were stable after these temperature cycles, were centrifuged at 5,000 rpm for 30 min and observed for phase separation, creaming or cracking. Formulations which showed no phase separation were exposed for three freeze thaw cycles between -21^{0}C and +25 ^{0}C with storage at each temperature for not less than 48 h. The formulations were then observed for phase separation[14].

Cloud point measurement

The cloud point measurement was carried out for the stable formulations as reported earlier [15]. The formulation was diluted up to 100 fold with distilled water and kept in a water bath which was maintained at a temperature of 25 °C with gradual increase of temperature at a rate of 5 °C/min and the corresponding cloud point temperatures were recorded at first sign of turbidity by visual observation.

Determination of the emulsification time

In order to determine the emulsification time (the time needed to reach the emulsified and homogeneous mixture, upon dilution), 1 g of each formulation was added to 200 mL of 0.1N HCl at 37 ◦C with gentle agitation using magnetic stirrer. The formulations were assessed visually according to the rate of emulsification and the final appearance of the emulsion.

Droplet size, particle size distribution and zeta potential analysis

One gram of SNEDDS formulation containing 25 mg of sertraline HCl was diluted to 100 mL with distilled water in a flask and was mixed gently by inverting the flask. The droplet size, zeta potential and the polydispersity index (PDI) of the SNEDDS formulations were determined by photon correlation spectroscopy that analyze the fluctuation in light scattering due to the Brownian motion of the droplets as function of time using a ZetasizerNano series (Malvern Instruments, USA). Light scattering was monitored at 25 ^{0}C at a 90^0 angle [14].

Transmission electron microscopy

SNEDDS was diluted with distilled water at 1:100 ratios and mixed by slight shaking. A drop of diluted SNEDDS was applied to a 300 mesh copper grid and was left for 1 min. The morphology and structure of the nanoemulsion formed were studied using transmission electron microscopy (TEM). A combination of bright-field imaging at increasing magnification and of diffraction modes was used to reveal the form and size of the nanoemulsion.

Drug content

The total amount of drug in the formulation was analyzed by dissolving the formulation in 10 mL of ethanol. This solution was vortexed for 10 min in vortex mixture. The mixture was centrifuged at 15,000 rpm for 10 min. Then the supernatant was filtered through Whatman filter paper. The concentration of sertraline HCl in the filtrate was analyzed spectrophotometrically at 273.4 nm.

***In vitro* drug release study of SNEDDS**

The quantitative estimation of release was performed by *In vitro* dissolution study of all the formulations, which was determined using USP XXIV dissolution apparatus II. The paddles were rotated at 100 rpm. One gram of SNEDD formulations containing 25 mg of sertraline HCl was put in hard gelatin capsule (0 size). The dissolution vessel contained 900 mL of acetate buffer (pH 4.5) as the dissolution medium maintained at 37 ± 0.5 ^{0}C. A 5 mL sample was withdrawn at 5, 10, 15, 30, 45 and 60 minutes. The withdrawn sample was replenished with 5 mL of fresh blank medium. The withdrawn samples were filtered and analyzed for the drug spectrophotometrically at 273.4 nm. Optimized formulation release was compared with that of plain sertraline HCl to evaluate the release enhancement by SNEDDS.

RESULTS AND DISCUSSION

Solubility study

Most important criteria for selection of components in any formulation are their pharmaceutical acceptability and are prerequisite for exploiting the advantages of nanoemulsions. It has been established that only very specific pharmaceutical excipient combinations lead to efficient nanoemulsion formulations [16].

The solubility of sertraline HCl in different oils was determined, as for drug substances with a log P value around 3 to 5, there is no clear trend regarding the type of oil that will cause the highest increase in solubility [17]. Solubility of sertraline HCl was determined in six different oils to choose the oil showing highest solubility for the drug. Results of solubility of sertraline HCl in various oils are shown in table 1 and The highest solubility of sertraline HCl was observed in PGML® (21.87 mg/ml), followed by Captex® (13 mg/ml) and Capmul® (10.51 mg/ml), hence these oils were chosen as oil phase for preparation of SNEDDS.

Also, results of solubility of sertraline HCl in various surfactants and cosurfactants are also shown in table 1. The solubility of sertraline HCl is highest in Tween 80® (59.40 mg/ml), followed by Cremophor® (32.50 mg/ml) and Transcutol® and hence these are chosen as surfactant and cosurfactant combinations for the preparation of SNEDDS.

Construction of ternary phase diagrams

Based on the results of solubility study, six phase diagrams were constructed, namely; system I: Capmul®/Cremophor®/Transcutol®; system II: Capmul®/Tween80®/Transcutol®; system III: Captex®/Cremophor®/Transcutol®; system IV: Captex®/Tween 80®/Transcutol®; system V: PGML®/Cremophor®/Transcutol® and system VI: PGML®/Tween 80®/Transcutol®. The phase diagrams are presented in figures 1-6. The shaded region indicates nanoemulsion

region. Wider region indicates better self-nanoemulsifying ability[18]. Ternary phase behavior investigations help to choose the proper concentration of excipients, i. e., oil proportion and optimum S/CoS ratio in the formulation to produce emulsions with good stability [19].

Table 1: Solubility of sertraline HCl in various oils, surfactants and cosurfactants

Components	Solubility (mg/ml)
Capmul®	10.51
Captex®	13.00
PGML®	21.87
Capryol®	0.16
Labrafil®	0.62
Cremophor®	32.50
Tween 80®	59.40
Polyethylene glycol	7.45
Propylene glycol	10.65
Transcutol®	29.41

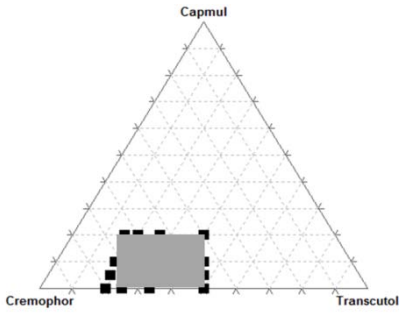

Fig. 1: Ternary phase diagram of SNEDDS containing Capmul®, Cremophor® and Transcutol® (gray domain indicates the region of self emulsification and black circles represent the stable formulations)

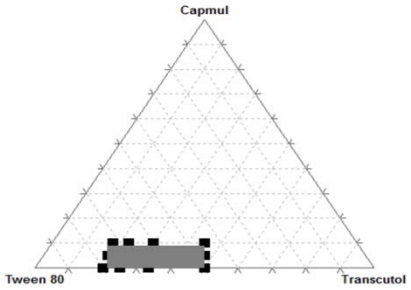

Fig. 2: Ternary phase diagram of SNEDDS containing Capmul®, Tween 80® and Transcutol® (gray domain indicates the region of self emulsification and black circles represent the stable formulations)

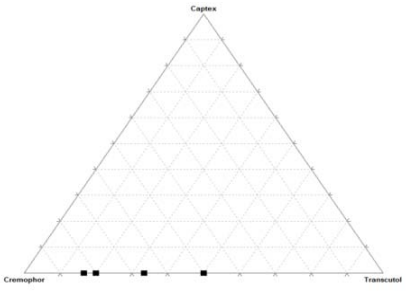

Fig. 3: Ternary phase diagram of SNEDDS containingCaptex®, Cremophor® and Transcutol® (black circles represent the stable formulations)

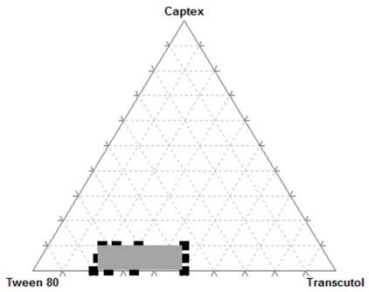

Fig. 4: Ternary phase diagram of SNEDDS containing Capmul®, Tween 80® and Transcutol® (gray domain indicates the region of self emulsification and black circles represent the stable formulations)

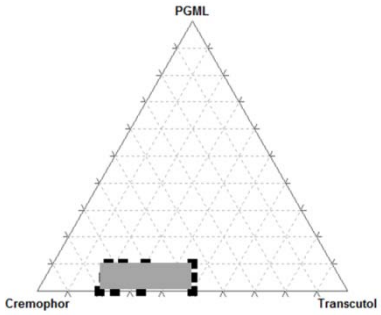

Fig. 5: Ternary phase diagram of SNEDDS containing PGML®, Cremophor® and Transcutol® (gray domain indicates the region of self emulsification and black circles represent the stable formulations)

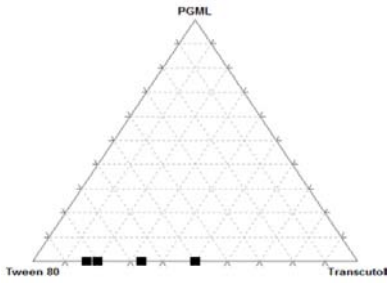

Fig. 6: Ternary phase diagram of SNEDDS containing PGML®, Tween 80® and Transcutol® (black circles represent the stable formulations)

In the current investigation, it could be seen that the system I shows the widest nanoemulsification region followed by systems II, III and IV, which showed the same area of nanoemulsification region. Systems V and VI show the least area of nanoemulsification region.

When Capmul® is used as the oil phase with Cremophor®; surfactant, the nanoemulsion area is much larger than that with Tween 80®. Cremophor®is a good emulsifier for the drug used in nanoemulsion, it may provide reduction in the surface tension and fluidizes the interfacial surfactant film which can expand the area of existence of microemulsion system [20]. Also Capmul®, a medium chain monoglyceride, is likely to increase the interfacial fluidity of surfactant boundaries in the micelles because of the entrapment of Capmul® in the high HLB surfactant, enhancing the emulsification process upon dilution with aqueous medium [21]. It was reported that medium chain monoglycerides (polar lipids) promote water penetration and self dispersibility of lipid formulations and have good solvent capacity for drugs [22].

The present study indicates that Cremophor® has better ability to emulsify PGML® than Tween 80®. Although, HLB values of both

surfactants used in the study are greater than 10, there is considerable difference in their ability to emulsify oils. Results obtained indicate that apart from HLB value, other factors such as the structure and the relative length of hydrophobic chains of surfactants influence nanoemulsification. These results are in conformation with results reported in literature [23]. The systems I, II, III and IV were selected based on the ability of the prepared ternary systems to form nanoemulsion containing the highest oil content (table 2).

Characterization of SNEDDS

Thermodynamic stability test

Thermodynamic stability studies were performed to observe the ability of the formulation to withstand different stress conditions. A stable SNEDDS formulation should not lose its ability of spontaneous emulsification upon dilution. All liquid formulations are found to be stable in the centrifugation test and in the freeze thaw cycle. There is no sign of phase separation. Results are shown in table 3.

Cloud point measurement

The cloud point is the temperature above which the formulation clarity turns into cloudiness. At higher temperatures, irreversible phase separation can occur due to dehydration of polyethylene oxide moiety of non-ionic surfactant and the cloudiness of the preparation would have a bad effect on drug absorption. Since both drug solubilization and formulation stability will decline with this phase separation, the cloud point of the formulation should be over 37 ^{0}C. The cloud point value is affected by factors such as drug hydrophobicity, kind, combination, mixing ratio and amount of each of the oils, surfactants and cosurfactants used [15]. In this study, cloud points of all formulations are high**.** Results contented the stability of formulations towards separation in the GIT temperature (table 3).

Determination of the emulsification time

The rate of emulsification was taken as an important index for the assessment of the efficiency of self-emulsification that is the SNEDDS should disperse completely and quickly when subjected to dilution under mild agitation[24, 25]. All the formulations exhibited a rapid rate of emulsification ranging from 10 to 39 s (Table 3). It is obvious that rapid emulsification is correlated with lower content of oil and higher content of Smix which results in lower viscosity of the system [25]. An attempt to find an adequate mathematical model between emulsification time and SNEDDS formulations failed. Gao et al.[26]reported a failed attempt to find an adequate mathematical model between droplet size and a SNEDDS formulation consisting of glycerol dioleate, glycerol monooleate, Cremophor®, and PEG 400.

Table 2: Composition of the prepared SNEDDS (%w/w)

Formula	Smix ratio	Capmul®	Captex®	PGML®	Cremophor®	Tween 80	Transcutol®
F1	1:1	10			45		45
F2	2:1	10			60		30
F3	3:1	10			67.5		22.5
F4	4:1	10			72		18
F5	1:1	20			40		40
F6	2:1	20			53.4		26.6
F7	3:1	20			60		20
F8	4:1	20			64		16
F9	1:1	10				45	45
F10	2:1	10				60	30
F11	3:1	10				67.5	22.5
F12	4:1	10				72	18
F13	1:1			10	45		45
F14	2:1			10	60		20
F15	3:1			10	67.5		22.5
F16	4:1			10	72		18
F17	1:1		10			45	45
F18	2:1		10			60	20
F19	3:1		10			67.5	22.5
F20	4:1		10			72	18

Table 3: Physicochemical properties of liquid SNEDDS

Formulation	Centrifugation test	Freeze thaw cycle	Precipitation After 6 h	Cloud point (Temp°C)	Self-emulsification time (s)
F1	√	√	√	72	15
F2	√	√	√	85	12
F3	√	√	√	82	10
F4	√	√	√	76	11
F5	√	√	√	74	23
F6	√	√	√	90	25
F7	√	√	√	92	24
F8	√	√	√	75	18
F9	√	√	√	71	17
F10	√	√	√	86	22
F11	√	√	√	92	10
F12	√	√	√	84	12
F13	√	√	√	77	15
F14	√	√	√	79	27
F15	√	√	√	81	29
F16	√	√	√	86	13
F17	√	√	√	90	10
F18	√	√	√	87	28
F19	√	√	√	76	29
F20	√	√	√	71	16

where, √- Passed and x- Failed

Droplet size, particle size distribution and zeta potential analysis

The droplet size of the nanoemulsion is a crucial factor in self-emulsification performance because it determines the rate and extent of drug release, as well as absorption [27]. The significance of emulsion droplet size in the *in vivo* performance of the formulation is not yet clear. Tarr and Yalkowsky[28]have demonstrated enhancement of the rate of intestinal absorption of cyclosporine through the reduction of the emulsion droplet size.

One possible explanation of the enhanced absorption observed with the small particle size is the larger surface area available for partitioning of the drug and for lipase activity. However, we fully agree to a recent statement by Pouton[29], that the role of droplet size is less important than it was assumed by some authors due to the fact that digestion will take place directly after the lipid dispersion leaves the stomach and at this stage particle size will have no or little effect. The results of droplet size determination and zeta potential of the different SNEDDS are shown in table 4.

Table 4: Globule size, PDI and Zeta potential of liquid SNEDDS

Formulation	Globule size (nm)	PDI	Zeta potential
F1	24.77 ± 2.56	0.71	-12.90
F2	25.43 ± 1.79	0.27	-10.96
F3	58.35 ± 1.18	0.30	-10.56
F4	70.42 ± 9.78	0.39	-15.23
F5	31.50 ± 3.69	0.33	-11.60
F6	20.10 ± 1.93	0.26	-11.26
F7	88.08 ± 1.62	0.50	-7.53
F8	92.46 ± 6.64	0.53	-9.64
F9	43.73 ± 5.78	0.33	-14.40
F10	29.20 ± 9.19	0.20	-11.19
F11	96.35 ± 16.12	0.31	-11.72
F12	120.15 ± 13.08	0.27	-12.10
F13	23.70 ± 4.52	0.49	-10.12
F14	26.64 ± 6.10	0.37	-11.20
F15	49.13 ± 2.31	0.43	-7.92
F16	58.00 ± 2.78	0.38	-9.93
F17	51.14 ± 7.78	0.32	-6.65
F18	49.55 ± 2.73	0.30	-9.50
F19	48.14 ± 3.34	0.27	-7.16
F20	64.29 ± 7.53	0.80	-7.77

Globule size of all formulations is in the range of 20.10-153.95 nm. Polydispersity index was determined which measures the spread of the particle-size distribution, in which a small value indicates a narrow particle-size range[30]. In general, the SNEDDS formulations exhibit a relatively limited size distribution, indicating a close size distribution**.**

Upon statistical analysis, there is no significant difference between the average globule size of all the four systems ($P > 0.05$). However, in system I, F1 and F2 show significant decrease in globule size compared to F3, F4, F5, F6, F7 and F8 ($P < 0.05$). In system II, F10 shows significant decrease ($P < 0.05$) in globule size compared to F9, F11 and F12. In system III, F14 shows significant decrease in globule size compared to F13, F15 and F16 ($P < 0.05$). In System IV, F18 and F19 show significant decrease in globule size compared to F17 and F20 ($P < 0.05$).

As described in literature, an increase in surfactant concentration results in the decrease in the droplet size, but this phenomenon levels off at a particular surfactant concentration, whereby any further increase in surfactant concentration results in a raise in droplet size [31]. Stabilization of oil droplets by virtue of decrease in droplet size can be attributed to localization of surfactant monolayer at the oil–water interface [32]. However, further rise in surfactant concentration leads to increased penetration of water into oil droplets causing breakdown of oil droplets and resulting in bigger droplets [16].

From the above analysis, it can be concluded that in most systems, the formula containing Smix ratio 1:1 or 2:1 shows the least globule size compared to the formulae containing Smix ratios 3:1 and 4:1. The reason may be due to higher surfactant concentration that results in more rapid maturation of the droplets.

The charge of oil droplets of SNEDDS is another property that should be assessed for increased absorption [31]. The charge of the oil droplets in SNEDDS is negative due to the presence of free fatty acids.

The significance of zeta potential is that it can be related to the stability of colloidal dispersions. Zeta potential indicates degree of repulsion between adjacent, similarly charged particles in dispersion. For molecules that are small enough, a high zeta potential will confer stability, i. e., the solution or dispersion will resist aggregation. Zeta potential controls charge interactions. Conventionally, a high zeta potential can be high in positive or negative sense, i. e., −30mV or +30mV would be considered as high zeta potential. Negative values of zeta potential of the optimized formulations indicate that the formulations are negatively charged and high values of zeta potential of all the formulations signify stability of the system [14].

Upon statistical analysis, there is no significant difference between the zeta potential of the SNEDDS formulations ($P > 0.05$).

According to the above results, F2, F6, F10, F14 and F19 were chosen for further investigation as they showed the smallest globule size.

Morphological characterization

Transmission electron microscopy is the most important technique for the study of microstructures, because it directly produces images at high resolution and it can capture any coexistent structures and microstructure transitions [33]. Morphology and structure of the optimized nanoemulsion formulations were determined using transmission electron microscopy (figure 7).

Combination of bright field imaging at increasing magnification and of diffraction modes was used to reveal the form and size of the nanoemulsion. The nanoemulsion droplets appear as dark and the surroundings were bright. Globules were seen as uniform in size and spherical in shape which indicates the good state of nanoemulsion.

Drug content

The drug content of sertraline HCl SNEDDS formulation was measured using UV spectroscopic method.

The drug content is determined by considering 25 mg of drug as 100%. All are in specified limit (97 %-101 %) of drug content (table 5).

***In vitro* drug release study**

The *In vitro* dissolution studies were also performed in order to ensure the quick release of the drug in the dissolution medium and they act as an important quality control tool for the dosage forms. Furthermore, *In vitro* dissolution studies also give an idea about the self-nanoemulsification efficiency of the developed system [34]. The results of sertalineHCl release from the prepared SNEDDS and plain drug are shown in table 6 and graphically illustrated in figure 8.

The release efficiency of drug from the SNEDDS formulations was significantly higher ($p < 0.05$) than the plain drug. This could be attributed to the small globule in case of nanoemulsion formulations which provided large surface area for the release of drug and thus permitting faster rate of drug release.

These results confirm the role of SNEDDS formulation to improve sertraline HCl solubilization and *In vitro* release.

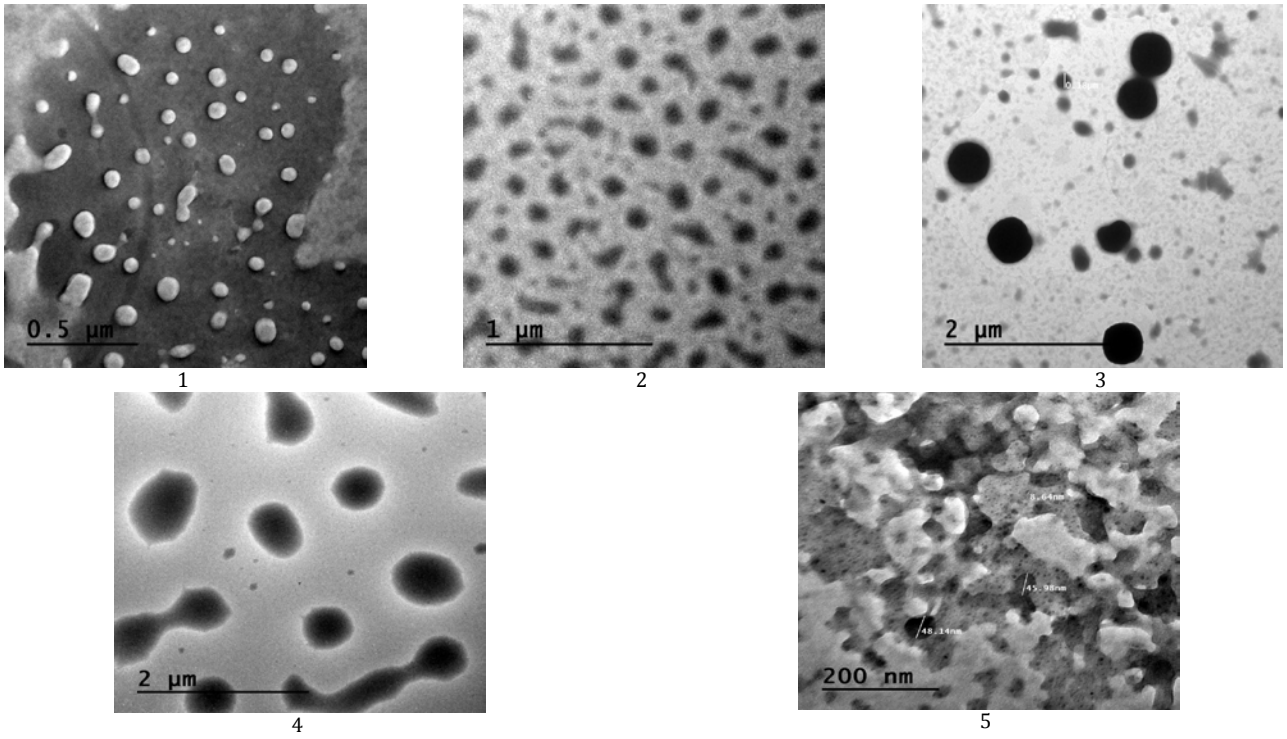

Fig. 7: Transmision electron microscopy of: (1) F2; (2) F6; (3) F10; (4) F14 and (5) F9

Table 5: Drug content of sertraline HCl in F2, F6, F10, F14 and F19

Formulation	Percent drug content (mean ± SD) from SNEDDS
F2	97.15 ± 2.15
F6	99.20 ± 3.78
F10	100.86 ± 5.91
F14	98.71 ± 2.46
F19	97.56 ± 5.74

Table 6: Release of sertraline HCl from F2, F6, F10, F14, F19 and the drug per se

Time (min)	Percent cumulative drug released (mean ± SD) from SNEDDS:					
	Plain drug	F2	F6	F10	F14	F19
5	42.26 ± 2.54	42.00 ± 3.60	36.60 ± 5.40	15.60 ± 2.40	39.60 ± 2.40	96.00 ± 0.09
10	46.80 ± 3.47	55.43 ± 3.62	65.60 ± 1.77	15.08 ± 1.81	50.02 ± 0.61	98.19 ± 0.02
15	58.09 ± 7.56	79.74 ± 6.04	73.16 ± 1.82	19.37 ± 1.22	54.49 ± 1.21	100.00 ± 0.05
30	62.01 ± 8.50	88.58 ± 7.27	80.17 ± 4.77	100.67 ± 6.25	100.30 ± 5.42	100.00 ± 0.97
45	71.95 ± 6.47	92.66 ± 7.91	87.81 ± 1.19	100.65 ± 2.97	100.43 ± 0.05	100.00 ± 0.07
60	74.75 ± 3.71	93.17 ± 6.15	100.89 ± 6.59	100.53 ± 1.18	100.10 ± 0.05	100.00 ± 0.04
Release efficiency (%)	**59.94 ± 5.21**	**78.36 ± 6.17**	**75.31 ± 1.60**	**80.38 ± 0.32**	**79.05 ± 0.45**	**95.15 ± 0.50**

In this study, sertraline HCl was formulated as SNEDDS in an attempt to increase its solubility and enhance its release. Screening of surfactants and cosurfactants studies helped to identify the most suitable excipients, whereas the phase diagrams gave a good idea about the concentrations of the nanoemulsion components that should be employed to achieve self-nanoemulsifying formulations. All the prepared SNEDDS were thermodynamically stable and globule size of all formulations was in the range of 20.10-153.95 nm. There was no significant difference between the average globule size of all the four systems ($P > 0.05$). The prepared SNEDDS showed

significant increase in the release profile when compared to plain drug. These results may shed a strong beam of light on the potentiality of utilizing SNEDDS for improving the biological performance of sertraline HCl.

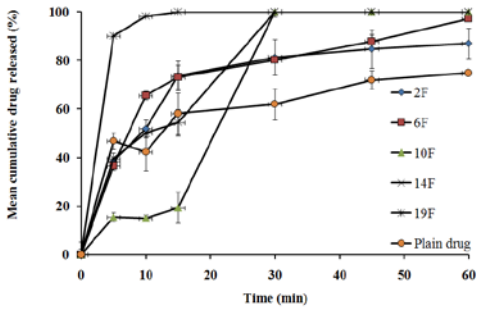

Fig. 8: Release profile of sertraline HCl from F2, F6, F10, F14, F19 and plain drugCONCLUSION

CONFLICT OF INTERESTS

Declared None

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