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Research Article

Spray dried self-nanoemulsifying drug delivery systems for sertraline HCl: Pharmacokinetic study in healthy volunteers

Abstract

Purpose: The aim of this study is to improvelow oral bioavailability of sertraline HCl by formulation and characterization ofsolid self-nanoemulsifying drug delivery system [SNEDDS] using spray drying technique.

Methods: Solubility of sertraline HCl in different vehicles was determined, and ternary phase diagrams were constructed.Various formulations were prepared and characterized by morphological characterization, differential scanning calorimetry and droplet size analysis. The formulations were evaluated for *in vitro* release profile in comparison to the marketed product [Lustral® tablets]. The in vivo study was performed on healthy human volunteers for pharmacokinetic analysis of the optimized formulations.

Results: *In vitro* release data showed significant improvement of dissolution rate of sertraline HCl in form of liquid SNEDDS compared to the plain drug. Optimized liquid SNEDDS were chosen for the preparation of solid SNEDDS by spray drying technique. High dissolution efficiency values of solid SNEDDS indicated the increase in dissolution characteristics of sertraline HCL in solid SNEDDS. F6 SNEDDS, comprising Capmul® 20%, Cremophor® 53.4%, Transcutol® 26.6% showed highervalues for AUC[0-72 h], AUC [0-∞] and AUMC[0-72h] compared to Lustral® tablets.

Conclusion: The prepared formulation reveals the potentiality of incorporating sertraline HCl in a SNEDDS formulation to improve the biological performance of the drug.

Introduction

Depression is the most familiar mental disorder that affects a large number of individuals in all countries. However, depression is under diagnosed and often under cured [1]. Recent research believes that depressive episodes may intensify severity of following episodes and may escalate theurgency for more health care resources, if left untreated.

Sertraline HCl – a selective serotonin re-uptake inhibitor – is indicated for the treatment of depression and anxiety disorders, panic disorder and post-traumatic stress disorder [2]. It is considered appropriate for the treatment of depressive symptoms in elderly patients, including those suffering from Alzheimer's disease, as it has minimal anticholinergic activity and is essentially devoid of cardiovascular effects [2].

However, sertralineHCl is practically insoluble in water and undergoes extensive first pass metabolism, resulting in poor bioavailability [40–45%]. Therefore, this required the drug to be taken in high doses in order to maintain adequate plasma levels [3]. Various problems are associated with its oral delivery such as gastrointestinal disturbances such as dry mouth, diarrhea, decreased appetite, nausea, impotence and insomnia [4]. In order to overcome the solubility problems, several formulation techniques can be approached. Among these techniques are self-nanoemulsifying drug delivery systems.

Nanoemulsions are isotropic systems, thermodynamically stable and the diameter of the droplets are within the range of 10-100 nm [5]. Self-nanoemulsifying drug delivery system is a pre-mixture of drug, oil, surfactant and cosurfactant that can be used to deliver drugs that are oil soluble. After gentle shaking and gastric juice dilution in stomach, it can form nanoemulsion spontaneously [6]. It is a suitable drug delivery system for oil-soluble drugs because it can be self-emulsified

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to nanoemulsion readily and steadily under mild condition in GI tract, providing large surface area for absorption and hence enhancing the bioavailability and lessening the irritation caused by the direct contact of the drug with GI wall. The pre-mixture can be stored for a very long period in capsules because of the high thermodynamic stability [7].

SNEDDS have the ability to decrease the slow and inadequate release of a drug, promote the formation of the solubilized phase and the extent of the transportation through intestinal lymphatic system, hence augmenting drug absorption from the GI tract [8].

Usually, the SNEDDS are prepared as liquid dosage forms. These liquid SNEDDS have to be administered in soft gelatin capsules. The major problems associated with soft gelatin capsules are the high production costs, poor stability, inadequate drug loading and low portability [9]. This shows the importance of the formulation of the solid SNEDDS which aims to merge the qualities of the conventional SNEDDS with those of solid dosage forms.

Several solidification techniques are used to prepare solid SNEDDS. Examples of these techniques are: adsorption to solid carrier, melt extrusion, spray drying, nanoparticle technology, etc. One of these techniques is adsorption to solid carrier which is considered one of the most uncomplicated and economical technique, which gives stable free flowing solid SNEDDS powder. It can be easily filled in hard gelatin capsule and easily disperses upon GI fluid contact [10].

Many recent studies have discovered that the solidification technique and selection of several solid carriers could negatively affect the size of the droplet of the solid SNEDDS and the concentrations of excipients therein [11]. However, there remains a lack of investigations on the effect of different types of solid carriers in solid SNEDDS formulations. It is also of great importance that the solidification procedure should conserve small droplet size for enhancing bioavailability of the formulated drug.

In this study, we have chosen to investigate the effect of spray-drying on the preparation of solid SNEDDS. It is a simple and inexpensive method commonly used for microencapsulation of drug components. In this study, we also elucidate the feasibility of dispensing sertraline HCl in liquid and solid SNEDDS for enhancing its bioavailability. The investigations include preparation, dissolution, characterization and pharmacokinetic evaluation of selected formulations.

Materials and Methods

Materials

Sertraline hydrochloride [sertraline HCl] was received as a gift sample fromHipharma Pharmaceuticals, Egypt. Transcutol® P [2-[2- ethoxyethoxy] ethanol], and Lauroglycol® 90 [propylene glycol monolaurate; PGML®] were obtained as a gift sample from Gattefossé, France. Sodium acetate and glacial acetic acid were purchased from El Nasr Pharmaceutical Chemicals, Egypt. Polyvinyl pyrrolidone K-30 [PVP] and lactose were purchased from Sisco Research Laboratories PVT.LTD, Bombay, India. Captex® 355 EP/NF [triglycerides of caprylic/capric acid; Captex®] and Capmul® MCM EP [glycerol monocaprylocaprate; Capmul®] were obtained as a gift sample from ABITEC Corporation, USA. Tween 80®[polyoxyethylene sorbitan mono oleate] was purchased from Oxford Laboratory Reagent, India. Cremophor® EL [PEG-35 Castor oil; Cremophor®] was kindly received from BASF, Germany.

Methods

Solubility study

The solubility of sertraline HCl in assorted oils, surfactants and cosurfactants was determined by adding an excess amount of drug to 2 ml of selected vehicles in 5 ml stoppered vials, and mixed using a vortex mixer. The vials were then kept at 25 ± 1.0 °C in an isothermal shaker for 72 h to attain equilibrium. The 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 the drug was determined spectrophotometrically at 273.4 nm.

Construction of ternary phase diagrams

According to 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®was used as cosurfactant. Oil, surfactant and cosurfactant were arranged in variuos combination for phase studies [12]. Surfactants and cosurfactant [Smix] were blended 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 examination was made directly for clarity, and precipitation of drug and excipients [13]. An aliquot [0.2 ml] of the formulation was added to 300 ml of double distilled water in a glass beaker at 37 °C, and the contents were mixed mildly with a magnetic stirrer at 100 rpm. The outcome emulsions were stored for 48 h at ambient temperature and observed for clarity, drug precipitation and coalescence of droplets. Emulsions showing phase separation, cracking or coalescence of oil droplets were judged as unstable emulsions. Phase diagram was designed to pinpoint the self-emulsifying region using Triplot v1-4 software.

Preparation of liquid SNEDDS of sertraline HCl

A group of liquid SNEDDS formulations were prepared using oil, surfactant and cosurfactant. Sertraline HCl [25 mg] was added to the mixture, and then the ingredients were mixed by mild stirring and vortex mixing, and heated at 37°C. The sample was stored at room temperature until further experimentaion [14].

Characterization of liquid SNEDDS

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 blended gently by inversion. The droplet size, zeta potential and the polydispersity index [PDI] of the SNEDDS formulations were investigated by photon correlation spectroscopy that inspects the fluctuation in light scattering

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due to the Brownian motion of the droplets as function of time using a Zetasizer Nano series [Malvern Instruments, USA] [15].

Morphological characterization: Liquid SNEDDS was diluted with distilled water at 1:100 ratios and mixed by slight shaking. One drop of diluted SNEDDS was applied to a mesh copper grid [300] and was left for 1 min. The morphology and structure of the nanoemulsion formed were inspected using transmission electron microscopy [TEM].

***In vitro* drug release study of liquid SNEDDS:** The quantitative evaluation of release was executed 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 each formulation; 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] and the temperature was kept constant at 37 ± 0.5 °C. A sample (5 mL) was withdrawn at 5, 10, 15, 30, 45 and 60 minutes. The collected sample was replenished with 5 mL of fresh blank medium. The collected 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 assess the release enhancement by SNEDDS.

Preparation of solid SNEDDS

A Büchi 190 nozzle-type mini-spray dryer [Flawil, Switzerland] was used for the preparation of solid SNEDDS. The hydrophilic solid carrier PVP or lactose [one gram] was dissolved in 100 ml water. The liquid SNEDDS [one gram] was added to these solutions with constant mixing, and the solution was continuously stirred at room temperature for 15 min. Each solution was delivered to the nozzle [0.7 mm diameter] at a flow rate of 5 ml/min using a peristaltic pump and spray-dried at inlet temperatures of 100 °C and 60 °C and outlet temperatures of 80 °C and 40 °C, respectively. The air pressure of the spray was 4 kg/cm^2. The direction of air flow was the same as that of the sprayed product.

Characterization of solid SNEDDS

Visual observation: In order to assess the emulsification properties, one gram of each formulation was introduced into 100 ml of distilled water in a beaker at room temperature and the content was mixed manually. The tendency to form a transparent or unclouded emulsion was evaluated as good, and when the formation was poor or milky in appearance, it was judged as bad. The prepared nanoemulsions were checked for 24 hrs for any sign of drug precipitation [16].

Robustness to dilution: Solid SNEDDS were diluted to 10, 100, 1000 times with different dissolution media, viz. water, 0.1 N HCl, and buffer with different pH values [1.2, 4.5, 6.8]. The diluted nanoemulsions were stored for 24 hr and observed for any sign of phase separation or drug precipitation [17].

Morphological analysis: The outer microscopic structures of solid SNEDDS formulations were examined using a scanning electron microscope with an image analysis system [ImageInsideVer 2.32]. The powders were fixed to a brass grid using double-sided adhesive tape, stained by 1% aqueous solution of phosphotungestic acid and observed after drying.

Solid state characterization by DSC: The thermal characteristics of sertraline HCl powder, PVP, lactose, physical mixtures and solid SNEDDS formulations were inspected using a differential scanning calorimeter [LabX XRD-6000, Shimadzu X-Ray Diffractometer, Japan]. About 2 mg of the samples were placed in sealed aluminum pans before heating under a nitrogen flow [25 ml/min] at a heating rate of 10 °C/min from 50 °C to 200 °C.

Assessment of droplet size, polydispersity index and zeta potential: One gram of solid SNEDDS formulation containing 25 mg of sertraline HCl was diluted to 100 mL with distilled water in a flask and was mixed gently. The droplet size, zeta potential and the polydispersity index [PDI] of the solid 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. Light scattering was monitored at 25 °C at a 90^0 angle [16].

***In vitro* drug release study of solid SNEDDS:** One gram of SNEDDS formulations containing 25 mg of sertraline HCl was put in hard gelatin capsule [0 size]. Optimized formulation release was compared with that of Lustral® tablets [25 mg] to evaluate the release enhancement by solid SNEDDS formulations.

In vivo study

Protocol: The design of this study composed of "An open label, randomized, three treatments, three periods, three sequences, single dose, crossover, balanced, comparative evaluation of relative bioavailability of test [two sertraline HCl-loaded solid SNEDDS formulations at a dose of 25 mg] and reference formulation [Lustral®, half of white capsular shaped 50mg sertraline hydrochloride film-coated tablets] in 6 healthy human subjects under fasting conditions". This study was approved by the research ethics committee for experimental and clinical studies at Faculty of Pharmacy, Cairo University.

Each individual orally administered a single dose of test and reference formulation with 240 mL of water after recommended wash out period of 14 days. Drinking water was restricted [at least] from 1 h before dosing and up to 2 h after dosing, supine position was restrained for four hours after dosing. Blood samples were collected in microcentrifuge tubes containing EDTA as an anticoagulant before [0.0 h] and at 1.0, 2.0, 3.0, 4.0, 5.0, 6.0, 8.0, 10.0, 12.0, 24.0, 48.0, 72.0, h of administration of drug. The collected blood samples were centrifuged at 2061×*g* for 10 min and plasma was separated, stored at -80 ^{0}C until drug analysis was carried out using LC/MS/MS.

The work was authorized and subjected to review by an Institutional Ethics Committee. All volunteers were informed of the aim and risk involved in the study and written consent were obtained. All the procedures while dealing with human subjects were based on International Conference on Harmonization, E6 Good Clinical Practice [ICH, E6 GCP] guidelines. Health check up was done by general physical examination or all subjects, ECG and laboratory tests like hematology and urine examination.

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Pharmacokinetic analysis

Noncompartmental analysis was performed by using WinNonlin® software [Pharsight Co., Mountain View, CA, USA] to calculate the pharmacokinetic parameters. Also, the area under the plasma concentration–time curve [AUC] was calculated using the linear trapezoidal method.

Results and Discussion

Solubility study

Solubility of sertraline HCl was detected in six various oils to choose the oil showing highest solubility for the drug. The solubility reusults of sertraline HCl in various oils are presented 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 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, oil fraction and optimum S/CoS ratio in the formulation to produce emulsions with good stability [19].

The nanoemulsion yielded by the use of Transcutol® as cosurfactant with either Cremophor® or Tween80®as surfactant could be obtained by 10-20% Capmul® oil. The concentration ranges of Cremophor® capable to produce nanoemulsion with 20% Capmul® were 45–64% and the ranges of Tween80® with 10% Capmul® were 45 to 72%. Cremophor® produced nanoemulsion with 10% PGML® oil, ranging from 45-72%. Also, when Tween80® was used as surfactant with 10% Captex®oil, the concentration of Tween80® ranged from 45-72%. In all the systems Transcutol® was used as cosurfactant.

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

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

When Capmul® is incorporated 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 the formulation; it may produceminimization in the surface tension and fluidizes the interfacial surfactant film which can broaden the range of existence of microemulsion system [20]. Also Capmul®, which is a medium chain monoglyceride, is expected to raise the interfacial fluidity of surfactant boundaries in the micelles because of the entrapment of Capmul®in the surfactant with the high HLB value, enhancing the emulsification process upon dilution with aqueous medium [21].

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 [17]. The systems I, II, IV and V were selected based on the ability of the prepared ternary systems to form nanoemulsion containing the highest oil content [Figures 1-4].

The different nanoemulsions showed no signs of phase separation. Hence, four different systems using 10-20% Capmul®as an oil phase, and Cremophor®as surfactant [F1–F8] or Tween 80® as surfactant [F9–F12], 10% PGML® oil and Cremophor® as surfactant [F13-F16] and 10% Captex® oil and Tween80®[F17-F20] were prepared, the results are shown in table 2.The prepared systems were subsequently subjected to characterization tests to select the best SNEDDS.

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 the release of the drug leading to enhancement of absorption [9]. From the results, 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 [23]. The charge of the oil droplets in SNEDDS is negative due to the presence of free fatty acids. The results of droplet size determination and zeta potential of the different SNEDDS are shown in table 2.

Morphological characterization

Transmission electron microscopy is the most important

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technique for the study of microstructures, because it directly produces images at sharp resolution and it can capture any present structures and microstructure transitions [24]. Morphology and structure of the optimizedformulations were determined using transmission electron microscopy [figure 5]. Combination of bright field imaging at increasing magnification and of diffraction modes was used to reveal the form and size of the nanoemulsion. The globules of the nanoemulsion 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.

In vitro drug release study

The *In vitro* dissolution studies were carried out in order to ensure the quick release of the drug in the dissolution medium and they act as a critical quality control tool for the dosage forms. Moreover, *In vitro* dissolution studies also give an idea about the self-nanoemulsification efficiency of the developed system [25]. The results are illustrated in figure 6.

The average release efficisency of drug from the SNEDDS formulations (80.31 %) was significantly higher [$p < 0.05$] than the plain drug (59.94 %). This could be associated to the small globule in case of nanoemulsion formulations which providedhigh surface area for the release of drug and thus permitting faster rate of drug release. These results support the role of SNEDDS formulation to enhance sertraline HClsolubilization and *In vitro* release. As a conclusion, F2 [Capmul® 10%, Cremophor® 60%, Transcutol® 30%], F6 [Capmul® 20%, Cremophor® 53.4%, Transcutol® 26.6%], F10 [Capmul® 10%, Tween80® 60%, Transcutol® 30%], F14 [PGML® 10%, Cremophor® 60%, Transcutol® 30%] and F19 [Captex® 10%, Tween80®67.5%, Transcutol® 22.5%] were chosen for the preparation of solid SNEDDS.

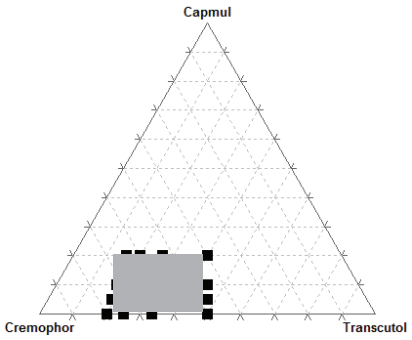

Figure 1: Ternary phase diagram of SNEDDS containing Capmul®, Cremophor® and Transcutol® (gray domain indicates the region of self emulsification and black squares represent the stable formulations).

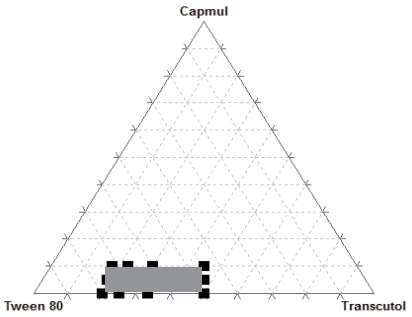

Figure 2: Ternary phase diagram of SNEDDS containing Capmul®, Tween 80® and Transcutol®.

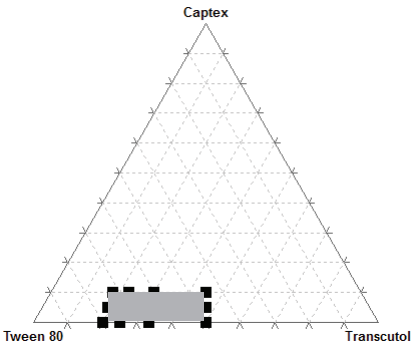

Figure 3: Ternary phase diagram of SNEDDS containing Captex®, Tween 80® and Transcutol®.

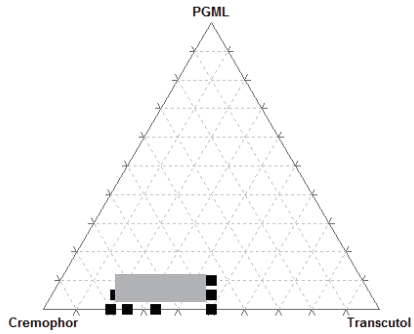

Figure 4: Ternary phase diagram of SNEDDS containing PGML®, Cremophor® and Transcutol®.

Preparation of solid SNEDDS

SNEDDS based formulations require filling into soft or hard gelatin capsules. Some of the problems encountered in the processing of liquid SNEDDS include leaching and leakage of the formulation, interaction with capsule shell components and handling complications for the manufacturers. Thus, it is of interest to incorporate the self-nanoemulsifying vehicles into a powder to design solid dosage forms which could present an attractive alternative to filledcapsulepreparations. The selection of the proper excipients, however, is crucial when dry adsorbed solidformulations are formulated. Different solid carriers can alter the release and absorption of drugs from solid SNEDDS, possibly through their influence on the size of the droplet. [26-28]

Characterization of solid SNEDDS

Visual observation: All formulations were observed for 24 hr at room temperature for clarity, phase separation and precipitation of drug. The formulations were categorized as clear [transparent or transparent with bluish tinge], non-clear [turbid], stable [no precipitation at end of 24 hr] and unstable [showing precipitation within 24 hrs] [29]. Despite the concentration of surfactant, all the batches were found to be clear, stable and showing no phase separation after 24 hours.

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Table 2: Composition of the prepared SNEDDS (%w/w), globule size, PDI and Zeta potential of liquid SNEDDS.

Formulation	Capmul®	Captex®	PGML®	Cremophor®	Tween 80®	Transcutol®	Globule size (nm)	PDI	Zeta potential
F1	10			45		45	24.77 ± 2.56	0.71	-12.90
F2	10			60		30	25.43 ± 1.79	0.27	-10.96
F3	10			67.5		22.5	58.35 ± 1.18	0.30	-10.56
F4	10			72		18	70.42 ± 9.78	0.39	-15.23
F5	20			40		40	31.50 ± 3.69	0.33	-11.60
F6	20			53.4		26.6	20.10 ± 1.93	0.26	-11.26
F7	20			60		20	88.08 ± 1.62	0.50	-7.53
F8	20			64		16	92.46 ± 6.64	0.53	-9.64
F9	10				45	45	43.73 ± 5.78	0.33	-14.40
F10	10				60	30	29.20 ± 9.19	0.20	-11.19
F11	10				67.5	22.5	96.35 ± 16.12	0.31	-11.72
F12	10				72	18	120.15 ± 13.08	0.27	-12.10
F13			10	45		45	26.70 ± 4.52	0.49	-10.12
F14			10	60		20	23.64 ± 6.10	0.37	-11.20
F15			10	67.5		22.5	49.13 ± 2.31	0.43	-7.92
F16			10	72		18	58.00 ± 2.78	0.38	-9.93
F17		10			45	45	51.14 ± 7.78	0.32	-6.65
F18		10			60	20	49.55 ± 2.73	0.30	-9.50
F19		10			67.5	22.5	48.14 ± 3.34	0.27	-7.16
F20		10			72	18	64.29 ± 7.53	0.80	-7.77

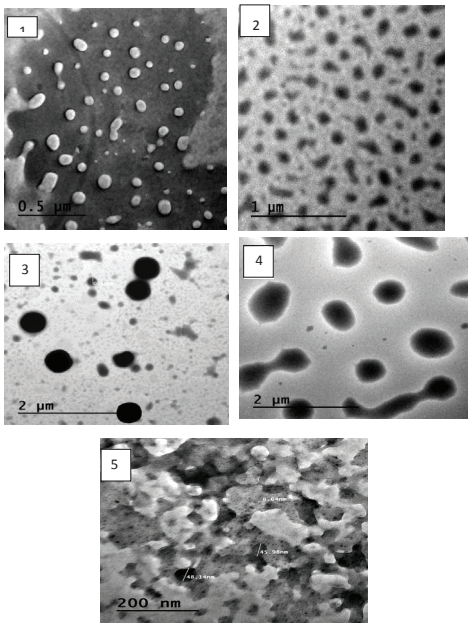

Figure 5: Transmision electron microscopy of: (1) F2; (2) F6; (3) F10; (4) F14 and (5) F9.

Robustness to dilution: Diluted nanoemulsions with various dissolution media, must stay robust to all dilutions, and should not separate or precipitate even after 24 h of storage [29]. Diluted SNEDDS did not show any precipitation or phase separation on storage in different dilution media. This shows that all media were robust to dilution.

Morphological analysis: In this technique, surface of the sample is scanned with a high-energy beam of electrons in a raster scan pattern [i.e., a rectangular pattern of image capture and reconstruction in television] [30]. The electrons interact with the atoms that make up the sample producing signals that involve information about the sample's surface topography, composition and properties like electrical conductivity. This technique is quite useful for determining the parameters like powder flow and compaction which influences the production of solid dosage forms [31].

The scanning electron micrographs in figures 7 and 8 reveal sertraline HCl as crystalline powder with irregular shaped crystals. The self-emulsifying powder showed smooth granular particles. No distinct crystals are evident on the surface of the particles after adsorbing the liquid SNEDDS on the surface of lactose or PVP.

Solid state characterization: DSC allows determination of thermotropic phase transition behavior in a quantitative manner. Thermal analysis technique has been extensively used to analyze the solid state characteristics of spray dried particles [32-34]. The thermograms recorded during analysis display pronounced melting peaks [figures 9 and 10].

Pure sertraline HCl shows sharp endothermic peaks at about 236 °C which infers the presence of crystalline form of drug. The physical mixture of the drug and lactose exhibits new endothermic peaks at much lower temperature of about 190 °C resulting from water bound in the molecules, which is indicated by the sharpness of the respective endothermic peak [35]. It could beexplained by the formation of crystalline microaggregates of the drug and their extensive dispersions within the mixture [36].

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The thermogram of PVP exhibits a broad endotherm ranging from 80 to 100 °C due to the water present. The DSC curves of the physical mixture can be considered to be the superposition of the DSC curves of the two separate components. Accordingly, these results reveal that absence of physical interactionbetween components within the mixture.

No representative peaks for drug are observed in SNEDDS, indicating the transformation of crystalline structure of sertraline HCl as it may be present in molecularly dissolved state or in amorphous form due to diminishing and disruption of crystal lattice and order.

Assessment of particle size, polydispersity index and zeta potential: The results of particle size determination and zeta potential of the solid SNEDDS are shown in table 3. Statistical analysis reveals that there is significant increase [P <0.05] in particle size of solid SNEDDS compared to liquid SNEDDS. The increment in mean particle size of the spray dried samples is apparently due to the increment in the solid content of liquid feed, and also increase in viscosity of the formulation. In addition, the presence of PVP could induce the adhesion of particles and develop agglomerate formation [37, 38]. Generally, during spray drying, large particle size of the samples reduces the escape of suspended fine particles in air from cyclone.

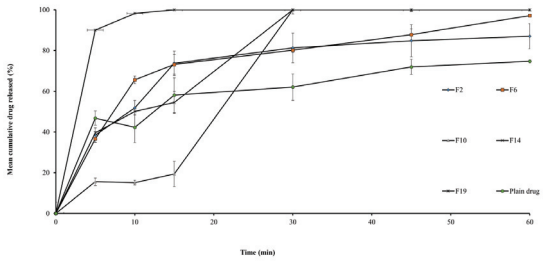

Figure 6: Release profile of sertraline HCl from F2, F6, F10, F14, F19 and plain drug.

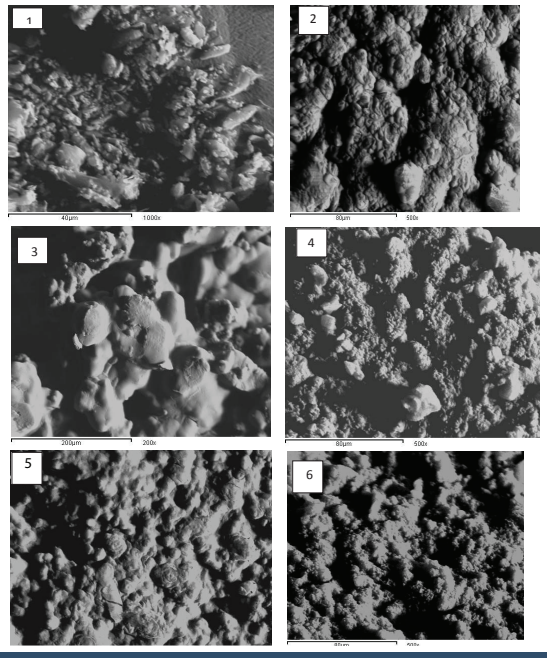

Figure 7: Scanning electron micrograph of SNEDDS prepared by lactose: (1) sertraline hydrochloride; (2) F2; (3) F6; (4) F10; (5) F14 and (6) F19.

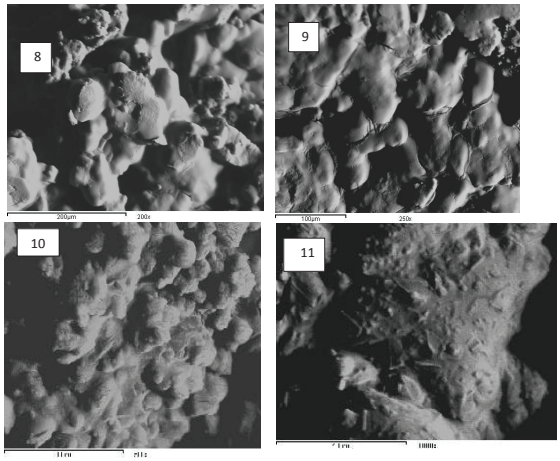

Figure 8: Scanning electron micrograph of SNEDDS prepared by PVP: (7) F2; (8) F6; (9) F10; (10) F14 and (11) F19.

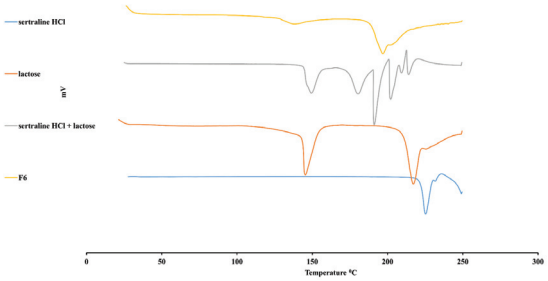

Figure 9: Differential scanning calorimetric thermograms of sertraline hydrochloride, lactose, physical mixture and F6.

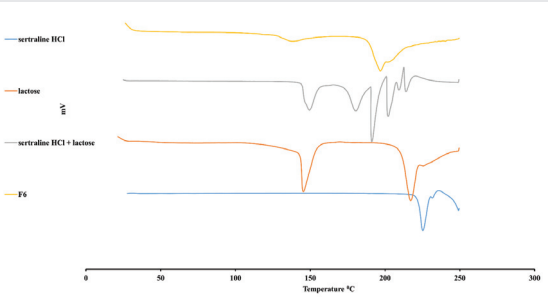

Figure 10: Differential scanning calorimetric thermograms of sertraline hydrochloride, PVP, physical mixture and F14.

Statistical analysis of solid SNEDDS prepared using lactose as carrier reveals that F6 shows the smallest particle size and PDI compared to the other formulations. When studying SNEDDS prepared by PVP as carrier, there is no significant difference [P >0.05] in particle size between F6 and F14; however, F14 shows significantly smaller [P <0.05] PDI values than F6. Also, F2 shows the smallest particle size when comparing it to the other formulations.

Comparison between the mean particle size of formulations using lactose and PVP reveals that formulations prepared with PVP show significantly smaller [P <0.05] particle size than formulations prepared with lactose.

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In general, zeta potential can be positive or negative in the range of -30 to +30 mV and the measured zeta potential of all solid SNEDDS lie within this range.

In vitro drug release study of solid SNEDDS

In the self-emulsifying systems, the required free energy to form an emulsion is low, therefore allowing formation of an interface spontaneously between the oil droplets and water. It is suggested that the oil/surfactant/cosurfactant and water phases swelleffectively, decreasing the oil droplet size and eventually increasing the release rate [39].

When studying the solid SNEDDS prepared by lactose [figure 11], it can be seen that F6, F14 and F19 show higher percentage of drug released after 15 minutes than F2 and F10. Also, F19 shows the highest [P <0.05] release efficiency (95.83 %), followed by F14 (93.80 %), F6 (83.55 %), F2 (67.08 %) then F10 (61.80 61.80).

Statistical analysis of solid SNEDDS prepared by PVP [figure 12], reveals that F14 shows the highest percentage of drug released after 15 minutes followed by F6, F19, F2 then F10. Additionally, F14 shows the highest [P <0.05] release efficiency (96.96 %), followed by F19 (93.64 %), F2 (80.14 %) then F10 (78.65 %).

Comparing the release efficiency of solid SNEDDS with Lustral® tablets (89.23 %) reveals that F14 and F19 prepared from both lactose and PVP show higher [P <0.05] release efficiency than Lustral®tablets; this could be due to the increased effective surface area and alteration in the native crystalline form of the drug.

Overall, SNEDDS prepared by PVP show higher [P <0.05] release efficiency than those prepared by lactose. This also agrees with the particle size results which show that SNEDDS prepared with PVP have smaller particle size than those prepared with lactose.

On the basis of these results, F6 prepared with lactose and F14 prepared with PVP were chosen for further investigation. F6 was chosen because it shows the smallest particle size and the lowest PDI in all SNEDDS prepared by lactose, also the release efficiency is comparable to that of Lustral® tablets. Although F2, F6 and F10, prepared with PVP, show smaller particle size than F14, the latter was chosen because it shows higher [P <0.05] release efficiency than Lustral® tablets and also lower PDI than other solid SNEDDS.

Table 3: Particle size, PDI and Zeta potential of solid SNEDDS.

Formulation (lactose as carrier)	Particle size (nm)	PDI	Zeta potential
F2	535.10 ± 36.91	0.58	-6.07
F6	168.00 ± 6.71	0.47	-17.00
F10	949.80 ± 52.36	0.84	-1.96
F14	731.40 ± 19.45	0.65	-1.36
F19	777.90 ± 56.02	0.55	-3.99
Formulation (PVP as carrier)	Particle size (nm)	PDI	Zeta potential
F2	110.50 ± 7.82	0.30	6.94
F6	198.90 ± 19.82	0.51	16.13
F10	172.80 ± 19.66	0.49	13.80
F14	199.80 ± 13.52	0.22	18.57
F19	372.50 ± 9.56	0.48	6.96

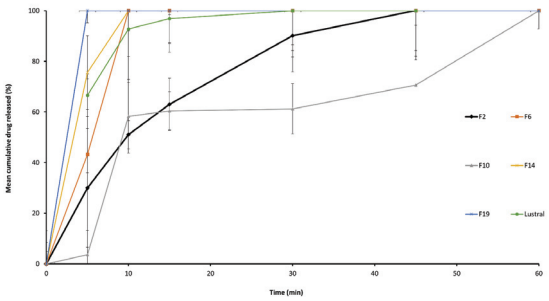

Figure 11: Release profile of sertraline hydrochloride from solid SNEDDS using lactose as carrier.

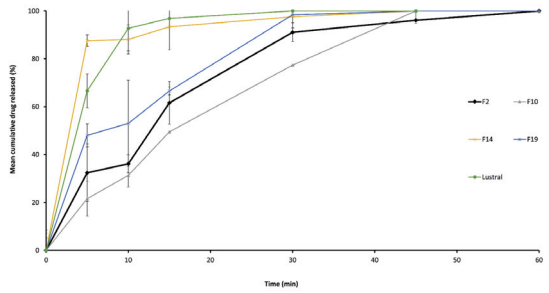

Figure 12: Release profile of sertraline hydrochloride from solid SNEDDS using PVP as carrier.

In vivo study

The LC–MS system consisted of an Agilent 1100 series [Agilent Technologies, Palo Alto, CA] binary pump, an autosampler connected to a TC–C18 column [5 µm, 150 × 4.6 mm i.d., from Agilent Technologies] and an Applied BiosystemsSciex API-4000Mass Spectrometer [Applied BiosystemsSciex, Ontario, Canada]. Oven temperature was maintained at 30 °C.The mobile phase was formic acid–10mM ammonium acetate–acetonitrile [1:299:700, v/v/v] delivered at 1.0 mL/min. An approximately 1:1 split of the column eluent was included so that 0.50 mL/min entered the mass spectrometer. The detector was maintained at unit resolution in the multiple reaction monitoring mode using the transitions of the protonated molecular ions of sertraline HCl at *m/z* 306.3 → 159.1.MS parameters were optimized by syringe pump infusing of a solution containing analyte and IS in mobile phase. Declustering potential and collision energy were 38 eV and 36 eV, respectively. The determined parameters were:curtain gas, gas 1, and gas 2 [nitrogen] had 15, 45, and 50units, respectively; dwell time 200 ms; source temperature 450 °C; ion spray voltage 1500 V.

Samples were vortexed thoroughly at room temperature and were employed as follows: 100 µL of internal standard [Azithromycin 200 ng/mL] and 100 µL[0.1% Ammonia solution] were added to 1 mL human plasma, vortexed for 30seconds, then 1.5 mL acetonitrile was added. The mixture

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was vortexedfor 30 seconds and centrifuged at 12,000 × *g* for 10 min, 10 µL of the supernatant was injected into the LC–MS–MS system for analysis.

As can be seen from the concentration time profile of sertraline HCl in figure 13, the concentration of the drug reached its peak followed by a fastdrop andthen it was raised leading to multiple peaks in the plasma concentrationtime profile. These multiple peaks could be attributed to the fact that sertraline HCl is excreted into bile after undergoing extensive glucuronidation in the intestine to sertraline carbamoyl-O-glucuronide. This could be due to that the drug is repeatedly delivered back to the site of action which is the lumen of the intestinal tract, via enterohepatic recirculation after undergoing reabsorption in the ileum [40].

The initial plasma concentrations of the drug in solid SNEDDS formulations were significantly higher [p<0.05] than in Lustral® tablets. Moreover, from 1 to 6 h, the plasma concentrations of the drug in F6 SNEDDS formulations were significantly higher [p<0.05] than in F14 SNEDDS formulations.

There was no significant difference between volunteers [inter-subject variation] [p>0.05] of the mentioned pharmacokinetic parameters [table 4].The value ofC_{max} for F6 SNEDDS [3.63 ± 0.49 ng/mL] was not higher [p>0.05] than Lustral® tablets [3.39 ± 0.43 ng/mL]. However, $C_{max}$for F14 SNEDDS [2.67 ± 0.55ng/mL] was lower [p <0.05] than that ofF6 SNEDDS and Lustral® tablets.

The T_{max} of F14SNEDDS, F6 SNEDDS andLustral® tablets were found to be 8 ± 1.96 h, 6± 0.81 h and 6± 1.96 h, respectively. Statistically, the T_{max} of F14 SNEDDS was higher [p < 0.05] than that of F6 SNEDDS or Lustral® tablets.

The difference between the values of MRT was not significant [p>0.05] when the value for F6 SNEDDS [28.16 ± 0.82 h] was compared with that of F14 SNEDDS[27.54 ± 2.94 h]. However, when the value of MRT for Lustral® tablets [24.24 ± 1.58h] was compared with that of F6 SNEDDS and F14 SNEDDS, it was found to be lower [p <0.05].These results may suggest that although the nanoemulsion could be promptly formed within minutes, the rate of release of free drug from the fine emulsified oil droplets or micelles formed at high concentration of the surfactant is comparably slow [41].

The values of half life time for Lustral® tablets, F6 SNEDDS andF14 SNEDDS were found to be 22.57 ± 5.62 h, 23.65 ± 4.20 h and 46.66 ±16.36 h, respectively. Value of half life time for F14 SNEDDS was found to be higher [p<0.05] compared to Lustral® tablets and F6 SNEDDS.

Statistical analysis revealed that there are significant differences[P <0.05] between $AUC_{[0-72\ h]}$ values for Lustral® tablets, F6 SNEDDS andF14 SNEDDS.$AUC_{[0-72\ h]}$ for F6 SNEDDS showed the highest value [128.37 ± 15.09 ng.h.mL^{-1}], followed by Lustral® tablets [79.59 ± 8.66 ng.h.mL^{-1}] and then F14 SNEDDS [60.47 ± 14.79 ng.h.mL^{-1}].

The difference in the values of $AUC_{[0-\infty]}$was not significant [p>0.05] when the value for F14 SNEDDS [90.47 ± 23.78ng.h.mL^{-1}] was compared with that of Lustral® tablets [90.18 ± 7.53ng.h.mL^{-1}]. However, the value of $AUC_{[0-\infty]}$ for F6 SNEDDS [141.06 ± 15.49ng.h.mL^{-1}] was found to be higher [p<0.05] in comparison to Lustral® tablets and F14 SNEDDS.

Statistical analysis showed that there is no significant difference [P <0.05] between $AUMC_{[0-72h]}$ for Lustral® tablets [1928.02 ± 218.92 ng.h^2.mL^{-1}]and F14 SNEDDS [1682.50 ± 524.44 ng.h^2.mL^{-1}]. Nevertheless, the value of $AUMC_{[0-72h]}$ for F6 SNEDDS [3611.77 ± 388.96ng.h^2.mL^{-1}] was found to be higher[p <0.05] in comparison to those of Lustral® tablets and F14 SNEDDS.

Regarding $C_{max}/AUC_{[0-\infty]}$, both Lustral® tablets and F14SNEDDSshowed higher values [p <0.05] [0.03 ± 0.002 h^{-1} and 0.03 ± 0.01 h^{-1} respectivelythan that ofF6 SNEDDS [0.02 ± 0.002 h^{-1}].

The K_e values forF6 SNEDDS and Lustral® tablets were 0.03 ± 0.009h^{-1} and 0.03 ± 0.005h^{-1}, respectively. These values were found to be higher [p <0.05] than that for F14 SNEDDS [0.01±0.008h^{-1}].

The pharmacokinetic results reveal that the prepared SNEDDS formulations enhanced the bioavailability of sertraline HCl compared with that of Lustral® tablets. This bioavailability increment indicates higher GI uptake of sertraline HCl SNEDDS [F6] in comparison to Lustral® tablets, although the SNEDDS formulation did not significantly alter the C_{max} compared with the tablet [p>0.05]. Thus, sertraline HCl SNEDDS [F6] was able to bypass first pass metabolism in order to reach systemic circulation.

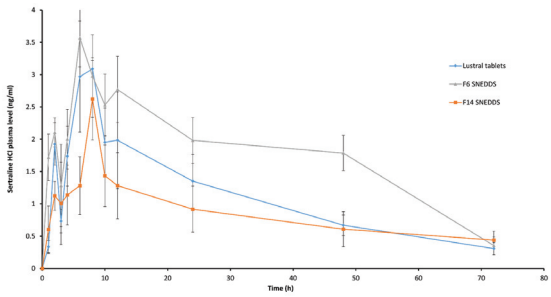

Figure 13: Mean plasma levels of sertraline hydrochloride after treatment of volunteers with Lustral® tablets, F6 and F14 SNEDDS.

Table 4: Pharmacokinetic parameters for sertraline hydrochloride formulations.

Parameter	Lustral® tablets	F6 SNEDDS	F14 SNEDDS
C_{max} (ng/mL)	3.39 ± 0.43	3.63 ± 0.49	2.67 ± 0.55
T_{max} (h)	6 ±2.33	6 ± 0.81	8 ± 1.96
MRT (h)	24.24 ± 1.58	28.16 ± 0.82	27.54 ± 2.94
Half life (h)	22.57 ± 5.62	23.65 ± 4.20	46.66 ± 16.36
$AUC_{(0-72\ h)}$ (ng.h.mL^{-1})	79.59 ± 8.66	128.37 ± 15.09	60.47 ± 14.79
$AUC_{(0-\infty)}$ (ng.h.mL^{-1})	90.18 ± 7.53	141.06 ± 15.49	90.47 ± 23.78
$AUMC_{(0-72h)}$ (ng.h^2.mL^{-1})	1928.02 ± 218.92	3611.77 ± 388.96	1682.50 ± 524.44
$AUMC_{(0-\infty)}$ (ng.h^2.mL^{-1})	3069.15 ± 656.20	4994.22 ± 945.92	6043.16 ± 2404.93
$C_{max}/AUC_{(0-\infty)}$(h^{-1})	0.03 ± 0.002	0.02 ± 0.002	0.03 ± 0.01
K_e(h^{-1})	0.03 ± 0.009	0.03± 0.005	0.01 ± 0.008

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The improved bioavailability of SNEDDS may be also due to its lymphatic transport through transcellular pathway [42]. It is also reported that the long-chain oils enhance lipoprotein synthesis and consequent lymphatic absorption [43]. The single layer of epithelial cell of the intestine is considered the main rate-limiting barrier for drug absorption/diffusion. The enhanced permeability could be due to high content of surfactants in SNEDDS which caused disturbing of the cell membrane. Surfactant likewise exhibited a reversible effect on the opening of tight junction; it may interact with the polar head groups found in the lipid bilayers, altering hydrogen bonding and ionic forces between these groups. Surfactant may also insert itself between the lipophilic tails of the bilayers, causing disruption of the lipid-packing arrangement [44,45]. Surfactants can also weaken the interfacial surface tension and augment the penetration of sertraline HCl.

Also, the presence of a surfactant in the nanoemulsion system has caused changes in membrane permeability by the inhibition of an apically polarised efflux system, which might cause enhancement of the oral absorption [45]. Not only is the bioavailability of sertraline HCl improved, but also SNEDDS form emulsion in GI fluid under mild agitation caused by GI motility. This lipid emulsions have advantages in terms of high drug loading capacity and reduction in irritation or toxicity of the incorporated drug. [46] .

Moreover, the emulsion droplets lead to a more uniform and rapid distribution of drug in the GI tract. The mucosal irritation is minimized due to the contact between the drug and the gut wall [47].

Discussion

In this study, the liquid SNEDDS of sertraline HCl were prepared then the optimized formulations were spray dried using lactose and PVP as solid carriers. The solid SNEDDS consisted of smooth granular particles, DSC analysis suggested that the drug in the solid SNEDDS is in the molecularly state or in the amorphous state. *In vitro* release study test showedthat the solid SNEDDS had a faster release ratethan the Lustral® tablets. In vivo study in healthy volunteers showed that solid SNEDDS gave significant increase inthe bioavailability of sertraline HCl compared to the Lustral® tablets.

From all the afore-mentioned results, it is evident that we can throw a strong beam of light on the potentiality of incorporating sertraline HCl in a SNEDDS formulation to improve the biological performance of the drug, via enhancing the bioavailability of the drug as well as minimizing its side effects.

All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (Research Ethics Committee for experimental and clinical sciences at Faculty of Pharmacy Cairo University) and with the Helsinki Declaration of 1975, as revised in 2000 (5). Informed consent was obtained from all patients for being included in the study.

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