Original Article

Formulation And Evaluation Of Sertraline Hydrochloride Tablet By Self Micro-Emulsifying Drug Delivery System For Solubility Enhancement

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Abstract

The purpose of this research is to design and formulate the Self-micro emulsifying drug delivery system (SMEDDS) of poorly water-soluble drug Sertraline Hydrochloride (SRT). SRT is commonly used selective serotonin reuptake inhibitor for the management of a number of depressive disorders. Its applicability is limited because of extensive metabolism and poor oral bioavailability of 44 %. Solubility of SRT in different vehicles is determined with the help of which ternary phase diagrams were constructed. Capmul MCM C8 EP (as oil phase), Cremophore RH 40 (as surfactant) and Labrafil M 2125 CS (as co-surfactant) were selected for development of liquid (SMEDDS) formulation. The prepared system was characterized for globule size, TEM, transmittance study, stability analysis and permeability. The formulation was converted to solid by adsorption on Neusilin US2 to convert the system into tablet the most convenient route. Results of evaluation and characterization of formulated T SMEDDS of SRT were compared with those of pure drug. In-vitro dissolution study and comparison to that of marketed formulation indicates that Tablet of this formulation helps to improve the solubility.

Keywords: Self-micro emulsifying drug delivery system, Sertraline Hydrochloride (SRT), solubility, surfactant, bioavailability.

INTRODUCTION

In recent years, the sudden progress of novel innovation, which includes structure-based drug design (SBDD), combinatorial chemistry, and elevated rate screening, has hidden several molecules with dominant pharmacological activity [1]. Nowadays, an increasing number of drug entity are categorized by being poorly water soluble and tendency to be lipophilic, such tablets are considered as Class- II drugs via biopharmaceutical class structures (BCS). Many Class-II medications cause low dosage proportionality, considerable intra- and inter-challenge variability, and poor oral bioavailability [2]. In recent years, much consideration has been focused on lipid-based formulations to improve oral bioavailability of poorly water soluble drugs. Lipid based drug delivery systems consists of delivering a drug dissolved in a mixture of one or more excipients which may be a mono, di and tri-glyceride; lipophilic and hydrophilic surfactants and a co-surfactant. When a drug is delivered through lipid formulations, it remains in the dissolved state throughout its transit in the GI tract.

Self emulsifying or self-microemulsifying drug delivery system (SEDD/SMEDD) incorporates surfactants and co-surfactants with isotropic mixtures natural, modified, or synthetic oils.of isotropic mixtures of natural/changed or artificial oils. When these structures are exposed to GIT fluids, they spontaneously emulsify into oil-in-water microemulsion with globule sizes ranging from 20-200 nm [3]. They can be used for liquid as well as solid dosage

forms. SMEDDS enable more efficient drug transport through the intestinal aqueous boundary layer leading to improved bioavailability. Solid SEDDSs are being developed from liquid/semisolid SEDDS mainly by adsorption on solid carriers, spray drying, lyophilization, melt extrusion, and nanoparticle technology. Such powders / nanoparticles, which are referred to as SE nanoparticles /dry emulsions/solid dispersions, are usually further processed into other solid SE dosage forms or, alternatively, filled into capsules (i.e., SE capsules).

SRT (1S,4S)-4-(3,4-di chlorophenyl)-1,2,3,4- tetrahydro-N-methyl-1-naphthaleneamine, hydrochloride 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. SRT is also the second most effective serotonin reuptake inhibitor and one of the top ten pharmaceutical products sold worldwide [4]. It is known that SRT gives drawbacks, namely slow oral absorption, and decrease oral bioavailability (44%) due to its low solubility (3.8 mg/L) [5].

The objective of the present study was to develop a SMEDDS of SRT to improve its solubility. SRT is an ideal drug candidate to be formulated in the form of SEDDS, as the SEDDS will enhance the drug's water solubility, protect it from presystemic metabolism and increase its absorption by lymphatic transport [6] which could enhance the bioavailability of Sertraline. Solubility of SRT in different vehicles is determined with the help of which ternary phase diagrams were constructed. Capmul MCM C8 EP (as oil phase), Cremophore RH 40 (as surfactant) and Labrafil M 2125 CS (as co-surfactant) were selected for development of liquid (SMEDDS) formulation. Prepared SMEDDS formulations were evaluated for emulsification time, cloud point, globule size, zeta potential and drug content. The formulation was converted to solid by adsorption on Neusilin US2 to convert the system into tablet the most convenient route.

MATERIALS AND METHODS

Materials: Sertraline Hydrochloride (Cadila Pharmaceuticals,Ahemadabad, India), Crospovidone (S.D. Fine Chemicals, Mumbai) and Talc (S.D. Fine Chemicals, Mumbai)

Method:

Solubility study of SRT:

The solubility of SRT in numerous vehicles like herbal and modified oils, surfactant, co-surfactants and buffer solutions had been decided via usual shake flask approach. Accurately weigh, 25mg of SRT became delivered to every vial containing prewarmed 1g of vehicle, i.e. Oil, co-surfactant, surfactant. The vehicles that showed complete solubility of the initial aliquot of SRT (25 mg) in such vehicles received the subsequent aliquots; 25 mg of SRT was similarly brought and observed by heating and cyclomixing for 4-5 min, and the procedure was repeated for a number of times until the vehicles were saturated with SRT. The total amount of SRT used to make the vehicles saturated is given, and the estimated solubility of SRT in each vehicle is determined. Each vial containing 5g of prewarmed chosen vehicle, such as oils, co-surfactants, and surfactants, had extra SRT added to it (more than the estimated solubility). The vials had been shaken for 48h in an incubator shaker (Remi, Mumbai, India), maintained at 37 ± 2°C, after finishing stroke of 48h of shaking, mixture become stored (24h) at room temperature to settle down the insoluble SRT. Aliquot from the filtrate suitably diluted with methanol and the solubility of SRT was decided by means of measuring absorbance with UV-Visible spectrophotometer at 273nm. Triplicate comparable samples had been considered for evaluation of every vehicle.

Construction of Ternary phase diagram

Ternary phase diagrams of oil, surfactant and co-surfactant have been plotted by using the use of flask inversion method [7]. The focus of each component was chosen based on Pouton's [5] requirements for spontaneously emulsifying systems i.e. 30-75% surfactant, 0-30 % co-surfactant, and 25% to 70 %. Different self-emulsifying blends

composition, have been chosen to create ternary phase diagram based on solubility studies and emulsification performance.

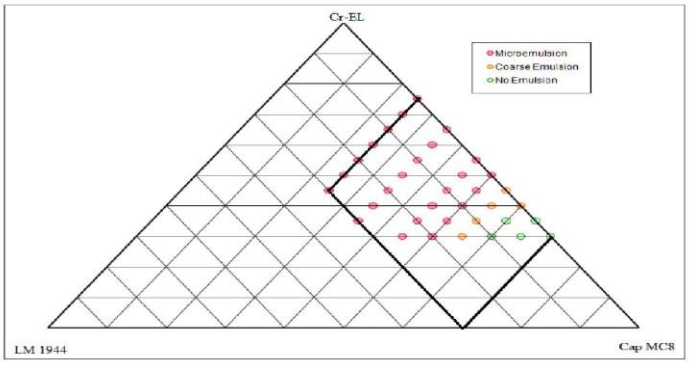

Fig 1: Ternary phase diagram of Cap MC8: Cr-EL: LM 1944 in distilled Water

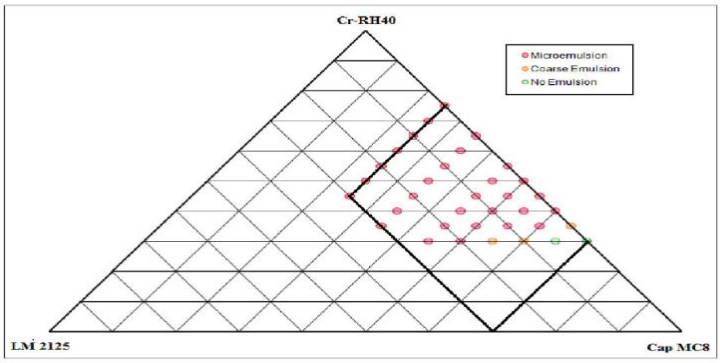

Fig 2: Ternary phase diagram of Cap MC8: Cr-RH40: LM 2125 in distilled Water

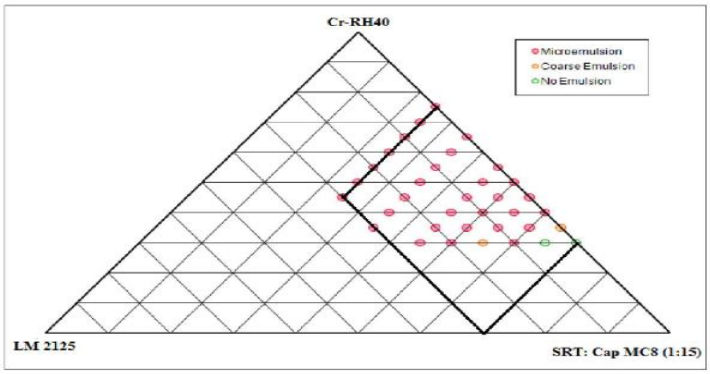

Fig 3: Ternary phase diagram of SRT loaded Cap MC8 (1:15): Cr-RH40: LM 2125 in 0.1 N HCl, pH 1.2 (SGF)

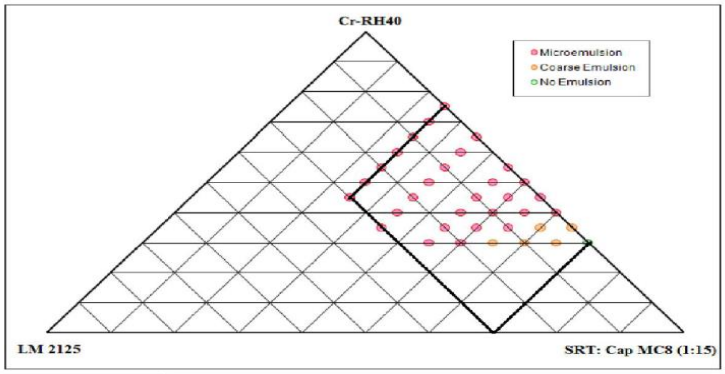

Fig 4: Ternary phase diagram of SRT loaded Cap MC8 (1:15): Cr-RH40:

LM 2125 in Phosphate buffer, pH 6.8 (SIF)

From the chosen combination i.e. Cap MC8: Cr RH-40: LM 2125, 9 distinctive method systems were decided on (based on ternary phase diagrams, systems containing most quantity of oily phase) to assess the ability of these mechanism to solublise the SRT. The selected formulation systems consist of oily segment: Cap MC8 within the range of 45% to 55% and surfactant combination: Cr RH-40 + LM 2125 in the range of 45% to 55%.

FORMULATION OF LIQUID-SMEDDS (L-SMEDDS) OF SRT

Based on the saturated solubility study of SRT, 4 different systems with maximum solubility of SRT were selected to develop L-SMEDDS by changing the concentration of Oil: Cap MC8, Surfactant: Cr-RH40 and Co-surfactant: LM 2125. SRT is available in various doses i.e. 28mg, 56mg and 112mg (equivalent to 25mg, 50mg and 100mg Sertraline base respectively), for the current study 28mg of SRT (equivalent to 25mg of Sertraline base) was used to limit the total formulation quantity [9]. SRT was added in the vial containing the respective amount of Cap MC8, this oily mixture was heated at 50 to 60°C in water bath. Respective quantity of prewarmed Cr-RH40 and LM 2125 was added and homogenized by cyclomixer for 10-15min resulting in isotropic system with complete SRT solublisation. The produce formulation was kept in room temperature till the further in-vitro evaluation. The optimized formulation of L-SMEDDS of SRT (380mg equivalent to 28mg SRT) was filled in hard gelatin capsule (Size "2") and stored at room temperature till the further use.

Table 1: Composition of SRT Liquid SMEDDS (L-SMEDDS) formulations

Components (mg) per unit formula	SRT L-SMEDDS Formulation code			
	SLS1	SLS2	SLS3	SLS4
Sertraline HCl	28.0	28.0	28.0	28.0
Capmul MCM C8 EP	158.4	158.4	158.4	176.0
Cremophore RH 40	158.4	140.8	123.2	105.6
Labrafil M 2125 CS	35.2	52.8	70.4	70.4
Mass fill per capsule(mg)	380.0	380.0	380.0	380.0

EVALUATION OF OPTIMIZED SRT L-SMEDDS (SLS2)

Globule size, polydispersity index and zeta potential

The L-SMEDDS, 50mg was diluted to 50ml with distilled water, SGF and SIF. The mean globule size, Polydispersity index (P.I.) and Zeta potential of the resulting microemulsion were determined by Malvern zeta sizer.

Table 2: Data of Globule size, Polydispersity index (P.I.) and Zeta potential of SLS_2 in various dilution media

Distilled water			0.1N HCl (SGF)			Phosphate buffer pH 6.8 (SIF)		
Globule Size (nm)#	P.I. *	Zeta potential* (mV)	Globule Size (nm)#	P.I. *	Zeta potential* (mV)	Globule Size (nm)#	P.I. *	Zeta potential* (mV)
60.19 ± 3.27	0.345	+ 13.12	65.23 ± 3.15	0.417	+ 14.23	61.19 ± 3.15	0.412	+ 14.09

Globule size is expressed as mean ± SD (n=2) P.I. and Zeta potential are expressed mean (n=2)

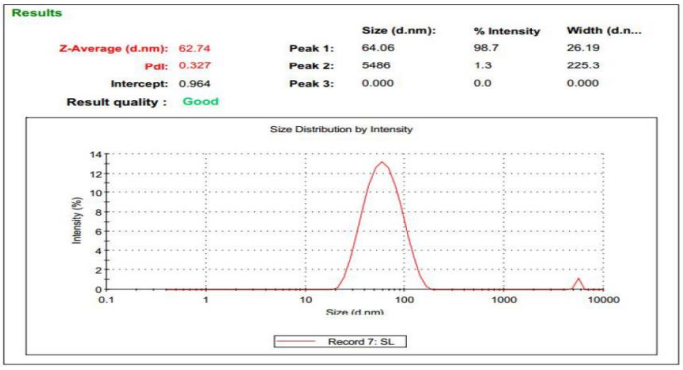

Fig 5: Globule size distribution and P.I. obtained from SRT L-SMEDDS (SLS2) in distilled water

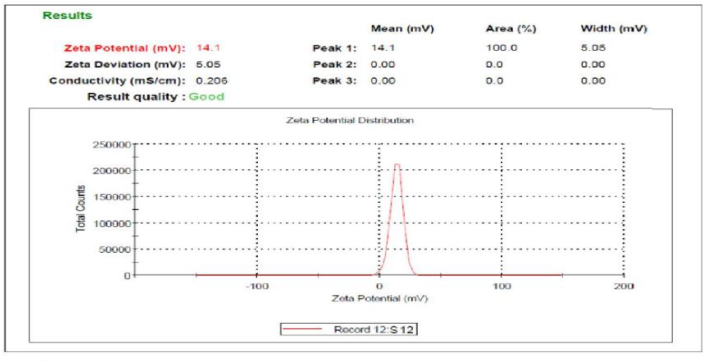

Fig 6: Zeta potential distribution obtained from SRT L-SMEDDS (SLS2) in Simulated gastric fluid

Transmission electron microscopy

The improved L-SMEDDS formulation after 1000 fold dilution in distilled water was investigated using Transmission electron microscopy. The image, confirms the ability of SRT L-SMEDDS to form spherical oil globules of nano size, the oil globules were evenly distributed over the film. This observation of TEM image is consistent with the result obtained from globule size investigation.

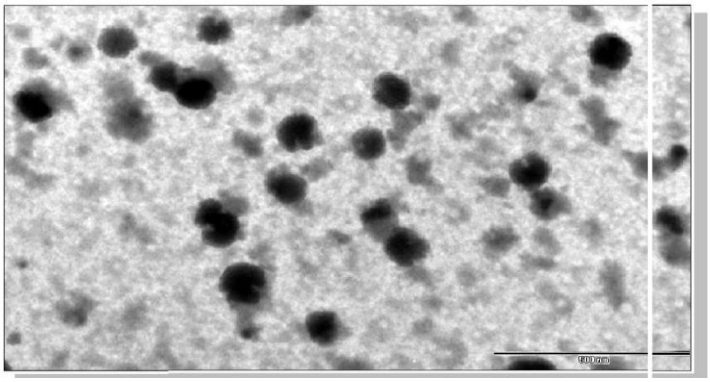

Fig 7: TEM image obtained from 1000 fold dilution of SRT L-SMEDDS (SLS2) in Distilled water

Drug content

In order to extract and solubilize the SRT, accurately weighed L-SMEDDS, equivalent to 28mg of SRT, were put into 50mL volumetric flask and allowed to dissolve in methanol for 15-20min The methanolic extract was refined using Whatman filter paper. The obtained filtrate finally diluted with 0.05 M Sodium acetate buffer pH 4.5 (SAB).The concentration of SRT was determined with the aid of measuring dA/dλ at 276.4nm with fresh SAB. Concentration of SRT was calculated using the calibration curve equation.

Procedure for in vitro dissolution

In vitro dissolution of simple SRT powder (28mg) and L-SMEDDS of SRT (equivalent to 28mg of SRT) packed in hard gelatin capsule were studied by use of USP equipment I at 37± 0.5°C with a rotating speed of 100rpm in media 0.05 M Sodium acetate buffer pH 4.5 (SAB). During the investigation, 5mL of aliquots were eliminated at predetermined time periods i.e.10, 20, 30, 45 and 60min from the dissolution medium and replaced with temperate buffer (SAB) to maintain a sink situation. The methonolic extract was filtered through Whatman filter paper. The amount of SRT released in the dissolution medium was determined by measuring dA/dλ at 276.4nm.The dissolution study was in other dissolution media specifically, 0.1 N HCl; [to Simulate Gastric Fluid (SGF)] and Phosphate buffer pH 6.8; [to simulate Intestinal fluid (SIF)] to examine the impact of pH on drug release [10, 11].

In vitro dissolution profile of optimized SRT L-SMEDDS (SLS2)

Table 3: In vitro dissolution profile of optimized SRT L-SMEDDS (SLS2)

Sr. No.	Sampling Time (min)	% Cumulative drug release *		
		Dissolution media		
		0.1N HCl	Sodium acetate buffer pH 4.5	Phosphate buffer pH 6.8
1	10	70.23 ± 3.24	73.19 ± 1.22	68.15 ± 2.21
2	20	87.37 ± 2.19	89.23 ± 2.43	86.12 ± 1.97
3	30	96.89 ± 1.27	97.19 ± 0.37	97.12 ± 0.49
4	45	100.07 ± 2.12	101.17 ± 1.11	101.12 ± 1.12
5	60	100.12 ± 1.21	101.23 ± 1.49	101.04 ± 2.23

* Values expressed as mean ± SD (n=6)

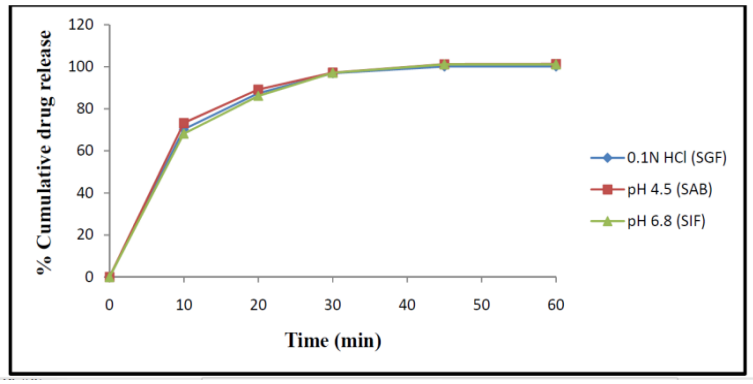

Fig 8: In vitro dissolution profile of SRT L-SMEDDS (SLS2) in various dissolution media

Transmittance study

By measuring transmittance, it was indicated that the L-SMEDDS (SLS2) produced fine-microemulsion in Krebs-Ringer buffer solution, because the resultant microemulsion seemed clear and transparent. Transmittance value of resultant emulsion was observed to be 98.56 %T.

Stability of SRT in Krebs-Ringer buffer solution

No SRT precipitation was observed in SRT solution and microemulsion before and after the storage of solutions for 2h in incubator. No significant changes, in SRT concentration in the Krebs-Ringer buffer solution was observed before and after 2h of storage at 37°C.

This result indicates that SRT was stable in Krebs-Ringer buffer solution.

Formulation of Powder SMEDDS (P-SMEDDS)

Optimized L-SMEDDS (SLS2) components converted into loose flowing powder via adsorption of liquid SMEDDS onto Neusilin US2 [12, 13, 14]. The acquired powder then dried at ambient temperature, saved at room temperature till the in addition reviews.

Development of SRT T-SMEDDS

Selection of Super disintegrating agent and optimizing its concentration

3 classically used super disintegrating agents Croscarmellose sodium, Crospovidone and sodium starch glycolate at 3 individual concentrations (1 %, 2.5% and 5% w/w) had been compared for their capability to disintegrate SRT T-SMEDDS with maintaining hardness of the tablet. The best disintegrating agent in terms of concentrations were assessed by examining the physical appearance of produced tablet slabs and monitoring the time required to completely disintegrate the T-SMEDDS. MCC was used as compressible diluents, while magnesium stearate and talc became brought as glidant and lubricant respectively.

Drug and tablet excipients compatibility study by FTIR spectroscopy

To confirm the compatibility of SRT with tablet excipients, FTIR spectrum of tablet blend was recorded using KBr pellet method; the obtained spectrum was analyzed and compared with the spectrum of plain SRT for the functional groups of the drugs to investigate the physicochemical compatibility.

Differential scanning calorimetric (DSC)

The DSC thermograms of plain SRT, physical mixture of SRT and Neusilin US2 (1:1w/w) and P-SMEDDS formulation were shown in Fig 10. Plain SRT showed sharp endothermic peaks at 128.1 and 246.4 °C indicating that the drug is highly crystalline. Neusilin US2 did not show any peak in the temperature range studied.

The physical mixture comprising equal amounts of Neusilin US2 and SRT showed a less intense endothermic peak at 219.4°C due to presence of crystalline SRT. The absence of obvious SRT peaks in the solid SMEDDS formulation indicates change in the melting behaviour of SRT and inhibition of crystallization following solubilisation using lipid surfactants and physical mixing with solid carrier

Based on the disintegration study, Crospovidone (2.5%w/w) was selected (Table5) as disintegrating agent. P-SMEDDS was blended with crospovidone and MCC, followed by addition of magnesium stearate (1% w/w) and talc (1% w/w), the obtained blend was then mixed thoroughly. The resultant powder mixture was compressed into tablet by using a single punch tablet machine using 12mm punch. Sufficient pressure was applied to keep the hardness of 4-4kg/cm2.

Table 4: Composition of optimized SRT Tablet-SMEDDS (SRT T-SMEDDS)

Ingredients	**Quantity per Tablet (mg)**	**Percentage (%)**	**Property**
SRT-L SMEDDS	380.00	58.45	Self emulsifying system
Neusilin US2	210.00	32.31	Adsorbing agent
Crospovidone	17.50	2.50	Super disintegrants
Magnesium Sterate	6.50	1.00	Glident
Talc	6.50	1.00	Lubricant
MCC	29.5	4.54	Directly compressible Diluents
Weight of Tablet (mg)	650	**100.00**	SRT T-SMEDDS

RESULTS

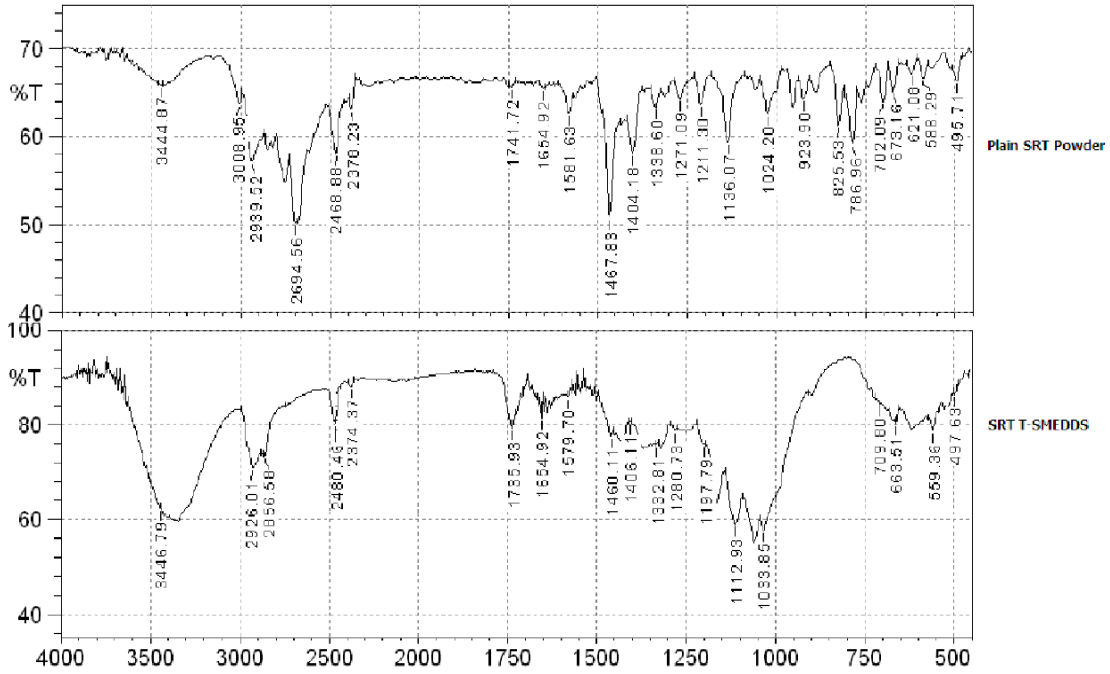

Fig 9: Comparative FTIR spectra of Plain SRT and SRT T-SMEDDS

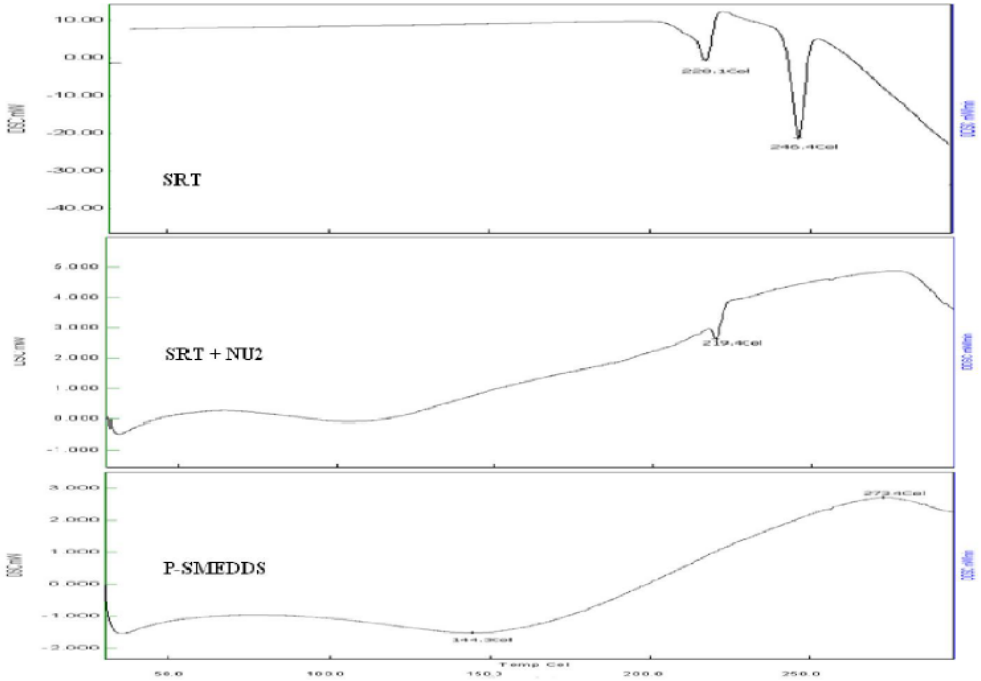

Fig 10: DSC thermogram of Plain SRT, SRT + Neusilin US2 (NU2) physicalmixture and P-SMEDDS

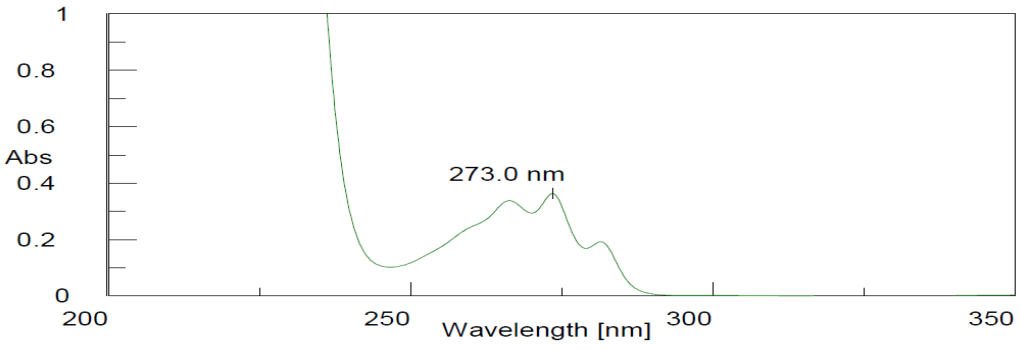

Fig 11: UV-Visible spectrum of SRT in methanol

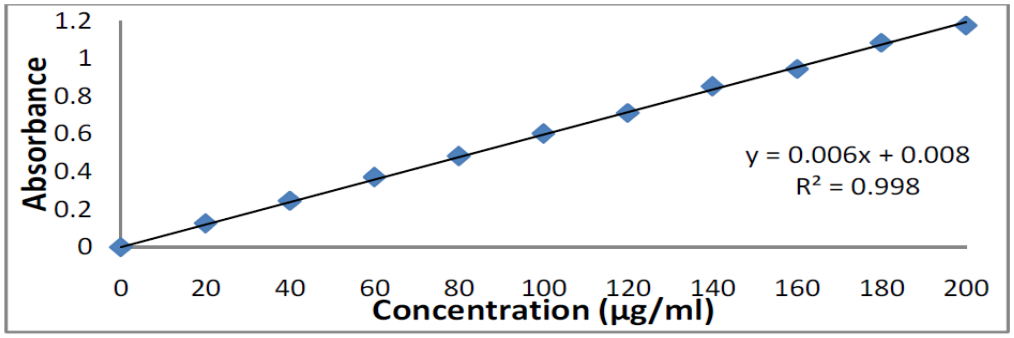

Fig 12: Calibration curve of SRT in methanol at 273nm

Table 5: Evaluation parameters of T-SMEDDS

Parameters	Observations	Inference
Drug content (%)*	102.52 ± 2.56%	Within the acceptable limit
Weight variation#	3.12%	Passes the test
Thickness*	4.2mm	Within the limit
Hardness*	4.5kg/cm2	Within the limit
Disintegration time*	2min 45s	Passes the test
Friability#	0.54%	Passes the test

* Values expressed as the mean ± SD (n=6)

Values expressed as observation made by using 20 tablets

Table 6: In vitro dissolution profile of SRT T-SMEDDS

Sr. No.	Sampling Time (min)	% Cumulative drug release *		
		Dissolution media		
		0.1N HCl (SIF)	SAB pH 4.5	PB pH 6.8 (SGF)
1	10	66.12 ± 1.21	71.07 ± 1.42	65.22 ± 1.10
2	20	85.09 ± 1.74	87.27 ± 2.08	84.87 ± 2.18
3	30	94.23 ± 0.22	96.47 ± 1.87	95.17 ± 1.54
4	45	101.12 ± 2.41	100.24 ± 0.14	100.23 ± 1.45
5	60	100.17 ± 2.23	101.65 ± 1.09	101.26 ± 1.36

*Values expressed as mean ± SD (n=6)

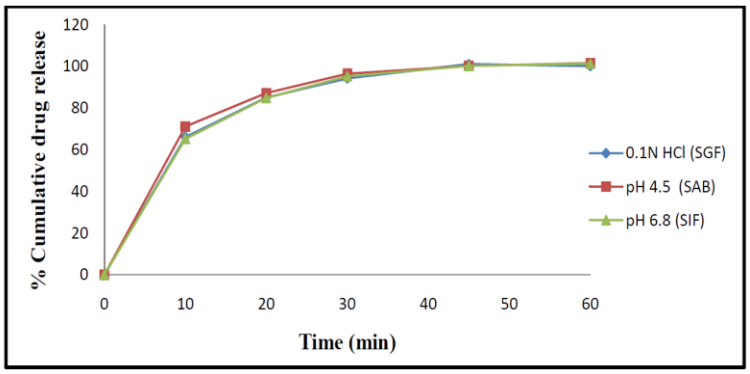

Fig 13: In-vitro dissolution profile of SRT T-SMEDDS in various dissolution Media

Table 7: In vitro dissolution profile of marketed SRT (28mg) tablet

Sr. No.	Sampling Time (min)	% Cumulative drug release *		
		Dissolution media		
		0.1N HCl (SIF)	SAB pH 4.5	PB pH 6.8 (SGF)
1	10	24.54 ± 0.89	28.07 ± 1.12	21.17 ± 1.17
2	20	39.09 ± 1.47	40.45 ± 2.47	37.07 ± 1.51
3	30	51.07 ± 2.45	53.41 ± 1.08	49.09 ± 1.18
4	45	62.17 ± 2.87	65.24 ± 0.18	63.23 ± 1.04
5	60	83.09 ± 2.07	87.08 ± 2.21	84.14 ± 2.23

*Values expressed as mean ± SD (n=6)

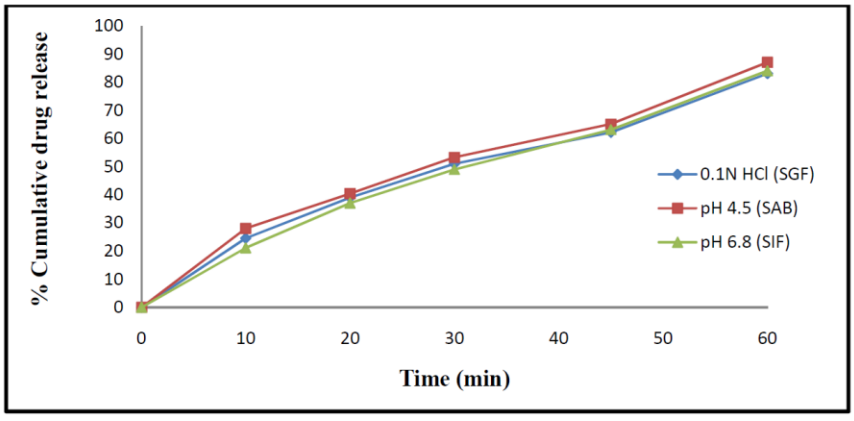

Fig 14: In vitro dissolution profile of SRT (28mg) marketed tablet in various dissolution media

Stability assessment of SRT-SMEDDS formulations

Table 8: Stability assessment of SRT L-SMEDDS (SLS2) at 40°C ± 2°C / 75% ± 5 % RH for 6 months

Parameters assessed	Study performed on				
	0th day	30th day	60th day	90th day	180th day
Physical appearance	Colorless, Clear and Isotropic	Colorless, Clear and Isotropic	Colorless, Clear and Isotropic	Colorless, Clear and Isotropic	Colorless, Clear and Isotropic
Compatibility with capsule shell	Stable	Stable	Stable	Stable	Stable
Drug content* (%)	102.27	100.21	99.68	98.17	97.56
DE* (Q20 min) in SGF	100%	99.23%	98.54%	96.30%	95.58%
FI* in DW	3	3	4	5	5
%T* in DW	101.28	99.68	99.56	98.45	95.12
Appearance in DW	Clear and transparent	Clear and transparent	Clear and transparent	Clear and transparent	Slightly bluish
Globule size# (nm) in D.W	60.87	60.13	62.61	64.85	70.54
P.I.# in D.W.	0.674	0.541	0.351	0.309	0.247

* Values are expressed as mean (n=3)
# Values are expressed as mean (n=2)

Table 9: Stability assessment of SRT P-SMEDDS (SPS2) at 40°C ± 2°C / 75 % ± 5 % RH for 6 months

Parameter assessed	Study performed on				
	0th day	30th day	60th day	90th day	180th day
Physical appearance	White colored, Non sticky	White colored, Non sticky	White colored, Non sticky	White colored, Non sticky	White colored, Non sticky
Compatibility with capsule shell	Stable	Stable	Stable	Stable	Stable
Drug content* (%)	102.54	101.07	98.57	97.12	94.56
DE (Q20 min)* in SGF	100%	101.23%	98.76%	95.77%	95.43%
Globule size (nm)# in D.W.	88.26	89.52	92.58	101.45	106.87
P.I.# in D.W.	0.546	0.487	0.322	0.323	0.347

* Values are expressed as mean (n=3) # Values are expressed as mean (n=2)

Table 10: Stability assessment of SRT T-SMEDDS (STS6) at 40°C ± 2°C / 75 % ± 5 % RH for 6 months

Parameter assessed	Study performed on				
	0th day	30th day	60th day	90th day	180th day
Physical appearance	Smooth surface	Smooth surface	Smooth surface	Smooth surface	Smooth surface
Hardness* (kg/cm2)	4.5	4.5	4.5	4.0	4.0
Drug content* (%)	101.25	100.65	98.56	96.14	95.22
Disintegration Time #	2min 45s	2min 45s	2min 45s	2min 30s	2min 30s
DE* (Q20 min) in SGF	100%	101.23%	97.54%	96.66%	95.34%

* Values are expressed as mean (n=3)

values expressed as mean (n=6)

DISCUSSION

SRT is a popular antidepressant whose poor water solubility limits its oral use. The present work was formulating a self microemulsifying formulation of SRT and evaluating its in vitro preparation. Solubility of SRT in oily phases and surfactants was determined to identify components of SMEDDS. Various surfactants and co-surfactants were screened for their ability to emulsify selected oily phase. Ternary phase diagrams were constructed to identify area of microemulsification for the selected systems. SMEDDS formulations were tested for microemulsifying properties and the resultant microemulsions were evaluated for clarity, precipitation, and particles size distribution. The optimized Liquid SMEDDS formulation was converted to solid dosage form (Tablet-SMEDDS) by adsorbing it on Neusilin US2. Crospovidone (2.5%) was selected as super disintegrating agent. SRT and selected excipients were found to be compatible by assessing it by FTIR and DSC study. L-SMEDDS and T-SMEDDS of SRT were found to be stable for 6 months at 40°C/RH 75%.Result of current research suggested that T-SMEDDS being the better alternative to the conventional SRT tablet formulation.

CONCLUSION

The aim of present study was to design and evaluate self-emulsifying drug delivery system (SEDDS) of poorly water soluble drug, SRT. A thorough survey of literature focused on drug delivery systems and drug profiles led to hypothesis that self micro-emulsifying drug delivery system (SMEDDS) could be used to improve the solubility of selected drugs. Drug solubility in various oil phases was studied by modifying routine shake flask method to identify self emulsifying components offering better drug solubility. The successful development of Self emulsifying drug delivery systems of poorly water soluble drug SRT could be accomplished through the present work. Liquid, Powder and Tablet dosage form of SRT was developed with scalable techniques. From the compiled results it can be concluded that formulation has significant improvement in solubility and rate and extent of dissolution in media simulating gastrointestinal fluids and also enhanced intestinal permeability would result in improved therapeutic performance, decreased doses and lesser cost of treatment.

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