Journal Of Harmonized Research (JOHR)

Journal Of Harmonized Research in Pharmacy
7(4), 2018, 89-97

ISSN 2321 – 0958

Original Research Article

DESIGN AND DEVELOPMENT OF SELF EMULSIFYING DRUG DELIVERY SYSTEM OF ZIPRASIDONE HYDROCHLORIDE

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Abstract: Ziprasidone is used in a treatment of schizophrenia, belongs to BCS class IIdrug (low solubility and high permeability). It undergoes extensive first pass metabolism with a bioavailability of only about 60%.The major drawback in the therapeutic application and efficacy of ziprasidone as oral dosage form is its low aqueous solubility. Hence this work was planned to improve dissolution characteristics of the drug by increasing its release and solubility through self emulsifying drug delivery system. In the study, self-emulsifying drug delivery system (SEDDS) of ziprasidone hydrochloride, a poorly soluble drug, was developed and evaluated by in-vitro techniques. Oil, surfactant, and cosurfactant were screened out according to their solubilizing capacity. Among the tested components Oleic acid, Tween-80, PEG 400 showed good solubilizing capacity. These three components were used in different ratios to prepare Ziprasidone SEDDS. The SEDDS formulations were transparent and clear. Droplet size of the emulsion was determined by Malvern Zeta sizer. Formulation F8 minimum mean droplet size (244.7nm). In-vitro drug release from F8 was higher (98% within 120 min) than other formulations. So SEDDS may be an alternative technique for the oral administration of Ziprasidone Hydrochloride.

Keyword: self-emulsifying drug delivery, oleic acid, tween 80, PEG 400, Ziprasidone Hydrochloride

Introduction: The oral route is one of the preferred routes for chronic drug therapy. Approximately 35- 40% of new drug candidates have poor water solubility. The oral delivery of such drugs is frequently associated with low bioavailability, high inter and intra subject variability and lack of dose proportionality. Efforts are going on to enhance the oral bioavailability of lipophilic drugs in order to increase their clinical efficacy.

To overcome these problems, new strategies were reported to increase solubility and bioavailability including complexation with

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Received on: May 2018
Accepted after revision: September 2018
DOI: 10.30876/JOHR.7.4.2018.89-97

cyclodextrins, solid dispersation (suspension), co precipitation, micronisation, salt formation, emulsion, use of micelles, and cogrinding. Emulsions are used as vehicles for the administration of drugs, especially due to its potential of enhancing the oral bioavailability of poorly absorbed drugs. [1]

Self-emulsifying drug delivery systems (SEDDS) are defined as isotropic mixtures of natural or synthetic oils, solid or liquid surfactants, or alternatively, one or more hydrophilic solvents and co-solvents/surfactants. [2]

Upon mild agitation followed by dilution in aqueous media, such as GI fluids, these systems can form fine oil in water (o/w) emulsions or microemulsions (SMEDDS). Self-emulsifying formulations spread readily in the gastro intestinal tract and the digestive motility of the stomach and the intestine provide the agitation necessary for self-emulsification.

SEDDS typically produce emulsions with a droplet size between 100 and 300 nm while SMEDDS form transparent microemulsions with a droplet size of less than 50 nm. An additional advantage of SEDDS over simple oily solutions is that they provide a large interfacial area for partitioning of the drug between oil and water. Thus, for lipophilic drug compounds that exhibit dissolution rate limited absorption, these systems may offer an improvement in the rate and extent of absorption and result in more reproducible blood time profiles and have been shown to enhance the oral bioavailability of lipophilic drugs.

Ziprasidone is used as an antipsychotic drug, belongs to BCS class II drug (low solubility and high permeability). It undergoes extensive first pass metabolism with a bioavailability of only about 60%.The major drawback in the therapeutic application and efficacy of ziprasidone as oral dosage form is its low aqueous solubility. Hence this work was planned to improve dissolution characteristics of the drug by increasing its release and solubility through self emulsifying drug delivery system.

Materials and Methods

Materials – Ziprasidone Hydrochloride was obtained as a gift sample from Ramdev chemical ltd, oleic acid tween 80 and PEG 400 was purchased from loba chemical. All the chemicals and reagents used were of analytical grade.

Solubility analysis of Ziprasidone Hydrochloride in various excipient- 500 mg of selected vehicles (i.e. oil/surfactant/co-surfactant) (Table 1) were taken in a screw capped vials. Excess amount of Ziprasidone was added to the mixture. The mixtures were shaken with shaker at 25 ^{0}C for 48 h. Once the equilibrium was reached each vial was centrifuged at 3000 rpm for 5 min, and the excess insoluble drug was discarded by filtration using membrane filter. The concentration of free drug was then quantified by the UV spectroscopy.

Table 1. List of vehicles (i.e. oil or surfactant or cosurfactant) used for solubility study.

Olive oil	Span 80
Oleic acid	Span 20
Castor oil	PEG 400
Lemon oil	Propylene Glycol
Tween 80	Glycerin
Tween 20	Ethanol

Formulation of SEDDS of Ziprasidone: SEDDS formulations were prepared using Tween 80 and PEG 400 as surfactant and co-surfactant with Mix ratio of 4:1, 3:1 (Table 2). The weight of the formulation was kept approx. 1000 mg. Level of Ziprasidone in all the formulation was kept constant (40 mg). Ziprasidone was accurately weighed and placed in a glass vial with the respective required quantity of oleic acid. The components were mixed by gentle stirring and vortex mixing. Respective quantity of surfactant and cosurfactant were added to the vial and mixed by vortex mixing. The mixture was stored at room temperature.

In vitro evolution of formulation-

1. Thermodynamic stability studies [3,4]: All developed formulations were subjected to 3 to 4 freeze-thaw cycles, which included freezing at – 4 °C for 24 h followed by thawing at 40 °C for 24 h. The formulations were then centrifuged at 3000 rpm for 5 min observed for phase and separation.

2. Self-emulsification assessment [5]: The self-emulsifying properties of SEDDS formulations were evaluated by visual assessment based on clarity and apparent stability of the resultant emulsion. SEDDS were added into 250 ml of distilled water and stirred magnetically at 100 rpm. The solution was then assessed visually for drug precipitation.

3. Drug precipitation assessment [3]: After 24 h visual inspection of the resultant emulsion (formed during self-emulsification assessment study) were performed for assessment of drug precipitation.

Table 2.Developed formulation with their compositions

Formulation code/ Components (mg)	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10
Ziprasidone	40	40	40	40	40	40	40	40	40	40
Smix ratio	**4:1**					**3:1**				
Oil: Smix	**1:1**	**1:2**	**1:3**	**1:4**	**1:5**	**1:1**	**1:2**	**1:3**	**1:4**	**1:5**
Oleic acid	480	320	240	192	160	480	320	240	192	160
Tween 80	384	512	576	614.4	640	360	480	540	576	600
PEG 400	96	128	144	153.6	160	120	160	180	192	200

The formulations were then categorized as clear (transparent), nonclear (turbid), stable (no precipitation at the end of 24 h), or unstable (precipitation within 24 h).

4. Viscosity determination [3,4]: SEDDS (0.5 g) was diluted 10 times with distilled water in a beaker with constant stirring on magnetic stirrer. Viscosity of the resultant microemulsion and initial SEDDS was measured using Ostwald viscometer.

5. Robustness to dilution [4,6]: 25 µl of SEDDS was diluted 10, 100 times with water in a beaker. The diluted microemulsions were stored for 12 h and observed for any signs of phase separation or drug precipitation.

6. Effect of pH of dilution media [7]: SEDDS was diluted to 10, 100 times with various dilution media like water, phosphate buffer, pH 1.2, pH 4.5, and pH 6.8. The diluted microemulsions were stored for 12 h and observed for signs of phase separation or drug precipitation.

7. Emulsion droplet size analysis [3,4]

SEDDS formulation was mixed with 250 ml of water in a beaker using a glass rod. The resultant emulsion was then subjected to globule size analysis using Malvern Zetasizer ZS (Malvern Instruments, Malvern, UK) with a particle size measurement range of 0.02 to 2000 µm. Globule size was calculated from the volume size distribution.

8. Drug Content: SEDDS containing 40 mg of drug was transferred in 50 ml of volumetric flask and the volume was made up with 50:50 ratio of methanol and distilled water. The drug was allowed to dissolve in the solvent for 30 min. than the solution was filtered and 1ml was taken in 10ml of volumetric flask and diluted up to mark with methanol. The resultant solution was analyzed spectroscopically at 317nm.The drug loading efficiency was determined by:

Drug loading efficiency = Amount of drug in known amount of formulation/ Intial dose 100*

9. *In vitro* dissolution studies [8]

In-vitro study was carried out using dialysis membrane 70 (Himedia). The dialysis membrane was activated prior using by soaking in 1% NaOH for overnight. Ziprasidone SEDDS (each equivalent to 40 mg of Ziprasidone) were placed in the donor compartment. The receptor compartment was

filled with dialysis medium (500ml of phosphate buffer 6.8 containing 0.5 % SLS). Whole assembly was put on magnetic stirrer (50 rpm) .At a fixed time interval, 5 ml of the sample was withdrawn from the receiver compartment through a side tube and the cell was replenished to their marked volumes with freshly prepared buffer solution and analyzed spectrophotometrically at 317 nm. Addition of solution to the receiver compartment was performed with great care to avoid trapping of air. The samples were filtered from filter paper and percent drug release was calculated.

10. Zeta potential determination [3]

Zeta-potential of SEDDS (1ml) diluted 10 times with distilled water was determined using the Zetasizer (Malvern Instruments, UK).

Stability Studies: The optimized SEDDS formulations (F8) were put into gelatin capsules (size 00) and subjected to stability studies at accelerated conditions of 40 °C/75% RH as per ICH guidelines. Samples were charged in stability chambers with humidity and temperature control. They were withdrawn at specified intervals for analysis over a period of 6 months for accelerated conditions. The charged samples were evaluated for self-emulsification capacity, drug precipitation assessment and emulsion globule size analysis.

Result and Discussion: Solubility Analysis

S.No.	Excipient	Solubility mg/ml
1.	**Oil**	
	emon oil	54
	Olive oil	33
	Castor oil	17
	Oleic acid	67
2.	**Surfactant**	
	Tween 80	32
	Tween 20	12
	Span 80	20
	Span 20	9
3.	**Cosolvent/cosurfactant**	
	PEG 400	68
	Propylene glycol	52
	glycerin	8

***In Vitro* Studies of Formulation**

Thermodynamic stability studies: Thermodynamic stability tests were performed to eliminate the metastable systems. Formulations were subjected to different stress tests, such as centrifugation, heating-cooling cycle, and freeze-thaw cycle tests.

Formulations F1to F4 (Smix ratio 4:1), F6 to F9 (Smix ratio 3:1) did not show any signs of phase separation. But formulations F5 and F9 separate out into two phases which may be due to the presence of less percentage of oil in the formulation. Also the high concentration of cosurfactant might have decreased the aqueous solvent capacity of the cosurfactant and might also have contributed for the drug to separate out resulting in the instability of the formulation.

Self-emulsification and Drug precipitation assessment: Self-emulsification ability of surfactants and cosurfactants was assessed to select the best ratio of Smix. Factors such as HLB value, structure and relative length of hydrophobic chains of surfactants had been reported to influence the micro-emulsification. The results of self-emulsification and precipitation studies are given in Table 3. F1-F4, and F6-F8 formed clear dispersion and did not show any drug precipitation and thus were considered as stable. Formulation F5 and F10 showed drug precipitation which may be due to the limited solubility of the percentage of oil present in these formulations. Since formulation F5 and F10 were not stable during thermodynamic studies and also exhibited drug precipitation so these formulation were excluded from further study. The self emulsification time of F1, F4, F6, and F7 higher than other so these formulations were also excluded from further study. Formulation F2 to F3, F8 and F9 were subjected to further evaluation.

Table 3. Self-emulsification and precipitation assessment data of formulations.

Formulation	F1	F2	F3	F4	F5
Self emulsification time	86 sec	30 sec	26 sec	148 sec	276 sec
Clarity	Clear	Clear	Clear	Clear	Clear
Drug precipitation	Absent	Absent	Absent	Absent	Present
Stability	Stable	Stable	Stable	Stable	Unstable

Formulation	F6	F7	F8	F9	F10
Self emulsification time	129 sec	85 sec	26 sec	41 sec	86 sec
Clarity	Clear	Clear	Clear	Clear	Clear
Drug precipitation	Absent	Absent	Absent	Absent	Present
Stability	Stable	Stable	Stable	Stable	Unstable

Viscosity determination

Viscosity is an important parameter for the evaluation of SEDDS. Initial viscosities of SEDDS were found to be very high but on dilution with water, viscosities of the respective systems were decreased. This suggests possibility of rapid absorption of SEDDS as viscosity of SEDDS will decrease on being diluted with body fluids inside. The viscosities of SEDDS are tabulated in

Table. 4. Viscosity determination

Formulation	F2	F3	F8	F9
Viscosity (cps)	216.8	216.1	215.8	214.2
Viscosity (cps) of diluted formulation	0.8872	0.8872	0.8872	0.8872

Robustness to dilution: Formulation F2 F3 F8 and F9, showed no signs of drug precipitation or phase separation on dilution of 10, 100 times. This implies that all the developed formulations were robust to dilution in the aqueous medium.

Effect of pH of dilution media: Formulations F2 F3 F8 and F9 were diluted 10, 100 times with various dilution media, viz. phosphate buffer, pH 1.2, pH 4.5, and pH 6.8. No sign of drug precipitation or phase separation was observed on storage in various dilution media which suggests that the various *in vivo* media are suitable for the release of the drug from SEDDS.

Table 5.Robustness to dilution and effect of pH of dilution media data of formulations.

	Formulation		F2	F3	F8	F9
Drug precipitation	Dilution with water	10 times	Absent	Absent	Absent	Absent
		100 times	Absent	Absent	Absent	Absent
	Dilution with pH 1.2 media	10 times	Absent	Absent	Absent	Absent
		100 times	Absent	Absent	Absent	Absent
	Dilution with pH 4.5 media	10 times	Absent	Absent	Absent	Absent
		100 times	Absent	Absent	Absent	Absent
	Dilution with pH 6.8 media	10 times	Absent	Absent	Absent	Absent
		100 times	Absent	Absent	Absent	Absent

Emulsion droplet size analysis: The droplet size of SEDDS is an important factor in self-emulsification performance as it determines the rate and extent of drug release as well as absorption. It is known that the particle size distribution is one of the most important characteristics of emulsion for the evaluation of its stability and also *in vivo* fate of emulsion. The smaller the droplet size, the larger the

interfacial surface area will be provided for drug absorption. [64]

Globule size and PDI for all the SEDDS have been summarized in Table 6.

Polydispersity index (PDI) is the ratio of standard deviation to the mean droplet size. This signifies the uniformity of droplet size within the formulation. The higher the value of polydispersity, the lower is the uniformity of the droplet size in the formulation. [65] PDI of most of the formulations was within the acceptable range except for formulations F8 which showed a higher PDI of 0.825. Among all the formulations F8 showed the minimum emulsion globule size of 244.7 nm with PDI of 0.702 followed by F2 with globule size of 251 nm with PDI of 0.738. Both these formulations showed emulsion droplet size within the theoretical globule size of microemulsion. So, formulations F2 and F8 were used for *in vitro* drug release studies.

Table 6- Globule Size of Formulation:

Formulation	F2	F3	F8	F9
Emulsion globules size (nm)	251	477.2	244.7	423
PDI	0.738	0.782	0.702	.825

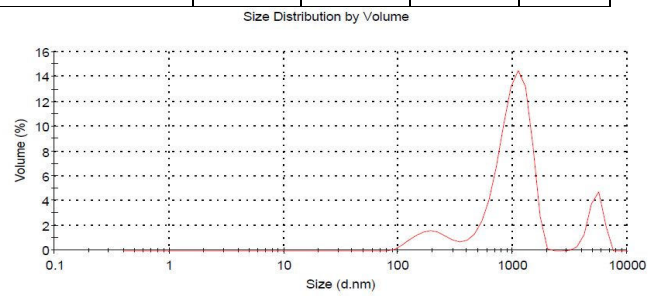

Fig-1 Globule size of F2.

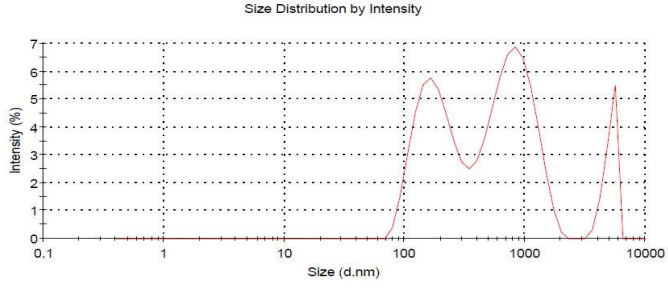

Fig-2. Globule size of F3

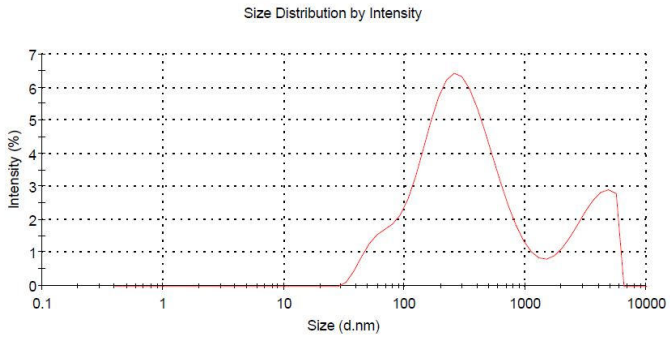

Fig-3 Globule size of F8

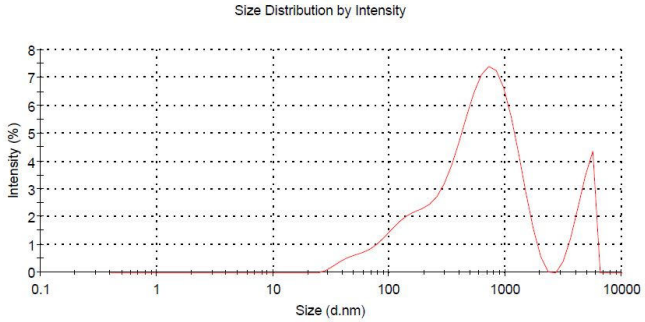

Fig-4 Globule size of F9

Drug Content- The drug content of formulation found to be 78.8 %.

***In vitro* Dissolution studies:** To understand the characteristics of drug release from SEDDS, an *in vitro* release study was carried out. *In vitro* dissolution profiles of Ziprasidone hydrochloride SEDDS in comparison to its commercial formulation are shown in Table 7 and in Fig. 7. Both SEDDS showed a very high and immediate drug release as compared to marketed capsule. At the end of 2h, F2 released (93.6%) and F8 (97.92%) as compared and marketed capsule (61.22%). Ziprasidone SEDDS showed an immediate burst in drug release followed by steady release and thus showed an improvement in the *in vitro* dissolution as compared to the marketed Ziprasidone capsule and in the dissolution media. It could be suggested that SEDDS resulted in spontaneous formation of microemulsion with smaller droplet size, which permitted a faster rate of drug release into the dissolution medium as compared to marketed formulation.

Formulation F8 showed a higher drug release as compared to F2 and also exhibited a smaller emulsion droplet size may be due to the presence of comparatively higher percentage of surfactant. So SEDDS formulation F8 was selected as an optimized formulation and further stability studies were carried out with F8.

Table 7. *In vitro* dissolution profiles of various ziprasidone formulations.

Formulation	Cumulative % drug release with time							
	10 min	20 min	30 min	40 min	50 min	60 min	90 min	120 min
F2	30.69	37.29	43.94	52.8	58.28	66.06	79.27	93.63
F8	32.40	36.013	44.61	53.23	60.14	68.92	81.98	97.92
Marketed Capsule	17.13	20.00	30.02	34.48	39.8	44.27	50.74	61.22

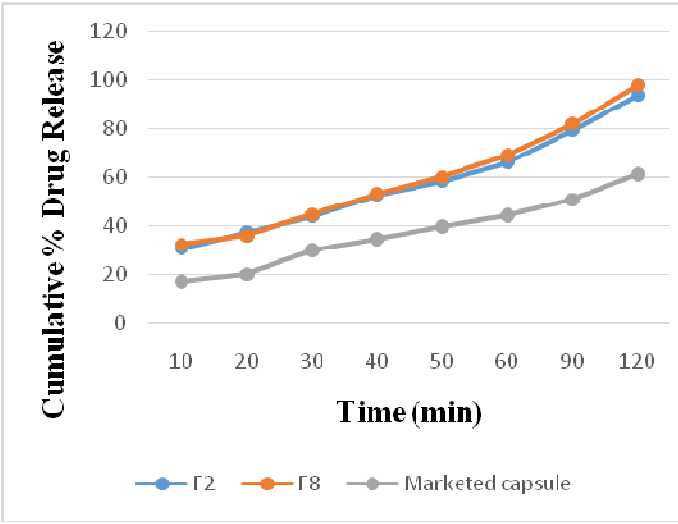

Fig 5- In vitro dissolution profile of formulations

Zeta potential determination: SEDDS F8 showed a negative zeta potential value − 6.85 as shown in Fig. 8, which indicates that negative charge particle do not affect the stability of microemulsion.

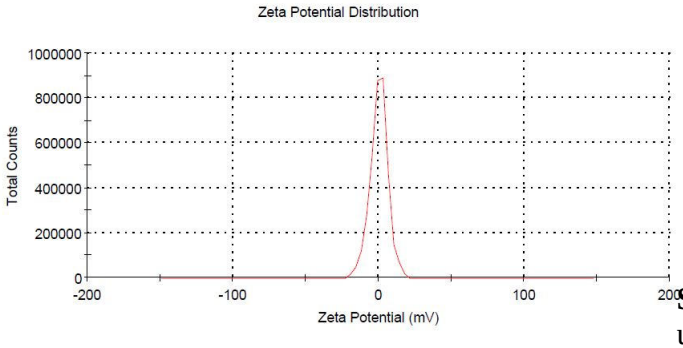

Fig. 6- Zeta potential value for SEDDS F2.

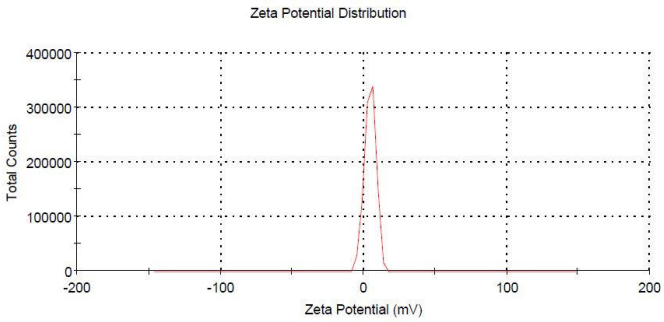

Fig. 7- Zeta potential value for SEDDS F3.

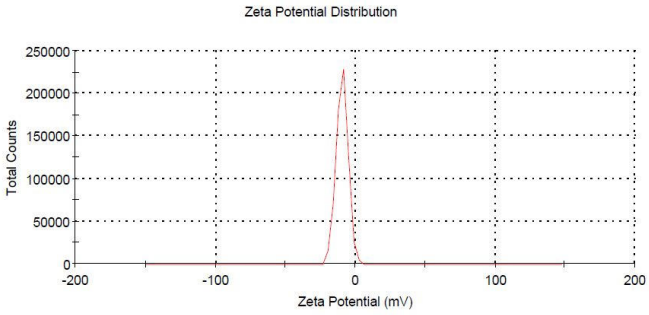

Fig. 8- Zeta potential value for SEDDS F8.

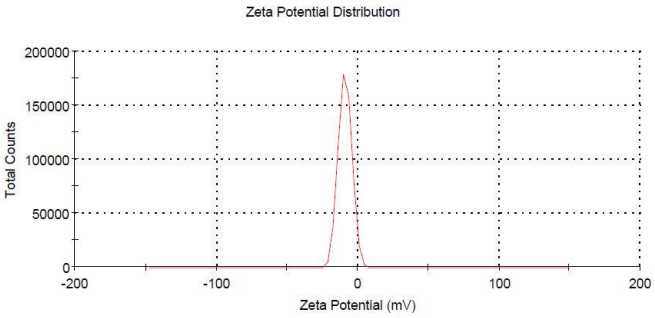

Fig. 9- Zeta potential value for SEDDS F9.

Stability studies: SEDDS formulations are usually put into gelatin capsules as the final

dosage form. But sometimes liquid filled gelatin capsules are susceptible to leakage and there are possibility for the precipitation of drug from SEDDS and phase separation. So, the SEDDS was subjected to accelerated stability studies to evaluate its stability and integrity of the dosage form. Table 8 gives the results of the stability samples withdrawn at the end of 1M.

There were no significant change in the droplet size and PDI of the SEDDS although a slight increase in the globule size, PDI has been observed which may be due to coalescence of the globules over period of time. All the SEDDS were found to form clear dispersion and none of the formulation showed any drug precipitation, capsule leak. These results confirm that the developed SEDDS were stable.

Table 8- Stability data of optimized SEDDS

Parameter	**1M**
Clarity	Clear
Drug precipitation	Absent
Stability	Stable
emulsion droplet size	245.1
PDI	0.702

Summary & Conclusion: Ziprasidone is used as an antipsychotic drug, belongs to BCS class II drug (low solubility and high permeability). It undergoes extensive first pass metabolism with a bioavailability of only about 60%.The major drawback in the therapeutic application and efficacy of ziprasidone as oral dosage form is its low aqueous solubility. Hence this work was planned to improve dissolution characteristics of the drug by increasing its release and solubility through self emulsifying drug delivery system.

The aim of the present study was to prepare and evaluate self-emulsifying drug delivery systems (SEDDS) of ziprasidone for treatment of schizophrenia. Following conclusions have been drawn from the present study: The analytical method developed for the estimation of ziprasidone was found to be sensitive and were successfully applied for the determination of respective drugs. Based on the solubility data, oleic acid was selected as oil phase, Tween 80 as surfactant, PEG 400 as co-surfactant for formulating SEDDS of ziprasidone. To determine the optimum concentration of oil, surfactant and co-surfactant for the formation of SEDDS, phase diagrams were constructed. The Smix ratio (Surfactant: Cosurfactant) of 4:1 and 3:1 showed the largest nanoemulsification region with infinite dilutions with water. SEDDS were formulated successfully with the selected concentrations of oil, surfactant, and cosurfactant for ziprasidone. Formulations F1 to F4 (Smix ratio 4:1), F6 to F9 (Smix ratio 3:1) were found to be thermodynamically stable and did not show any signs of phase separation. Ziprasidone SEDDS, F1 to F4 & F6 to F9 formed clear dispersions and did not show any drug precipitation and thus were considered as stable. All the above SEDDS were robust to dilution in the aqueous media. All the SEDDS on dilution with dilution media of varying pH did not show any drug precipitation or phase separation and the viscosity of the respective systems decreased upon dilution with distilled water. SEDDS of ziprasidone with Smix ratio of 3:1 exhibited a lower emulsion droplet size as compared to formulations with Smix ratio of 4:1. Among all the formulations F9 showed the minimum emulsion globule size of 244.7 nm with PDI of 0.702 followed by F3 with globule size of 251 nm with PDI of 0.738. Ziprasidone SEDDS (F2 and F8) showed a very high and immediate drug release as compared to marketed tablet. At the end of 2 h, F2 released (93.63%) and F8 (97.2 %) as compared to marketed capsule (61.2%). Formulation F8 showed a higher drug release as compared to F2 and also exhibited a smaller emulsion droplet size. The optimized formulations were found to be stable under accelerated conditions for 1 month with respect to self-emulsification, emulsion droplet size and absence of drug precipitation. In conclusion, the present study demonstrated successful preparation of self-emulsifying drug delivery systems of ziprasidone.

Future scope

- The pilot plant scale up studies is required for the optimized formulation to meet the industrial and regulatory requirements.
- The long term stability studies as per ICH guidelines are required to establish the stability data of these formulations.
- The formulations are to be studied in large number of healthy human subjects to establish the pharmacokinetic profile, safety and efficiency.
- The related technologies can be utilized to other classes of drugs with solubility problem and low and variable bioavailability.
- Extensive research in this SEDDS field is necessary w.r.t. mechanism of drug absorption through SEDDS.

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