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Formulation and Evaluation of Fast Disintegrating Tablets Containing Sertraline Solid Dispersion Using *Plantago Ovata*

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A B S T R A C T

The aim of the present research is to formulate Sertraline Hydochloride solid dispersion (SRT-SD) fast disintegrating tablets. The speed of onset of action of antidepressant drug is clinically important for several reasons. Fast disintegrating tablets of SRT-SD was formulated by using natural superdisintegrant adopting direct compression method to minimize time of onset of action and also become economic. The study describes formulation of solid dispersion of SRT using HPMC E5 as a carrier and further converting SRT-SD into fast disintegrating tablets utilizing *Plantago ovata* mucilage as natural superdisintegrant. All tablets formulations were evaluated for various pre and post compression parameters. The F1 batch showed release kinetics closest to Serta® with maximum r^2 (0.9991) value was considered to be the optimized batch and showed hardness of 3.10 kg/cm^2, disintegration time of 28.00 second and dissolution of 95 % in 12 min. The stability study clearly indicate that optimized batch can increase the disintegrating and dissolution time of SRT and utilized as prominent alternative for the treatment of depression.

Keywords: Sertraline HCl, Superdisintegrant, Plantago ovata, Solid dispersion.

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INTRODUCTION

Sertraline HCl (SRT) is a selective serotonin reuptake inhibitor (SSRI) that is used to treat depression and anxiety. SRT belongs to the Biopharmaceutical Classification System (BCS) class II drugs which are characterized by low water solubility and good permeability and also suffers from low bioavailability due to first-pass effect [1]. Therefore, solubility enhancement turns out to be prior requirement for improvement of oral bioavailability. To increase the solubility of SRT, solid dispersion (SD) technique is considered as one of the significant compared to other conventional methods [2].

Fast disintegrating tablets (FDTs) are considered as an ideal alternative of conventional tablet specifically for geriatric and paediatric patients, due to various advantages they provide like precise dosing, high drug loading, not require water to swallow and also they can be taken anywhere at any time. FDTs are a convenient option for travelling patients and diligent peoples who do not have immediate access of water hence patient compliance is improved. Additionally due to pre-gastric absorption the bioavailability of the drugs is increased and fewer doses are required [3, 4].

The disintegration of tablets has gotten extensive consideration as an important march to achieve rapid drug release. This leads to an accessible distribution and promotes faster release of the active ingredient. Relative rapid disintegration of tablets is important norm for determining the unrestricted dissolution manners of drugs [5, 6]. Polymers from natural sources are very viable and safe. They are effectively accessible in regular spaces of the world and are consequently more valuable than man-made polymers. Most drugs use natural polymers and are more successful than synthetic drugs [6]. Mucilage of *Plantago ovata* has been utilized as important natural excipient to get

a variety of functions in tablet formulations, additionally superdisintegrant property of *Plantago ovata* is widely studied and accepted [7-9].

So, the present study aimed towards solubility improvement of SRT by solid dispersion technique using HPMC E5 as a carrier. Further converting SRT-SD into fast disintegrating tablets utilizing *Plantago ovata* mucilage as natural superdisintegrant.

MATERIALS AND METHODS

Sertraline HCl was received as gift samples from Cipla Ltd., Mumbai, India. All the other excipients for FDT preparation were of analytical grade.

Drug and excipients compatibility studies

A compatibility study of drug with excipients is an early risk reduction strategy. It precludes the use of excipients which may interact with the drug substance. SRT was triturated with each individual excipient in the ratio 1:1. The samples were stored for four weeks 40°C/75% RH [10]. Physical evaluation of these mixtures was done to check the change in appearance.

Phase solubility study

In order to select the appropriate carrier for SRT solid dispersion this study was performed. Saturation solubility of SRT in HPMC E3, E5 and E15 was determined. The solutions were filtered and absorption was measured using UV spectrophotometer. Graph of solubility vs concentration of carrier was plotted. The Gibbs free energy for the solubilization was calculated using equation $\Delta G°_{tr} = -2.303 RT \log S_0/S_s$

Selection of solid dispersion method

To select the suitable method for preparation of solid dispersion, SRT-SD was prepared using drug/HPMC E5 in the molar concentrations of 1:1 by closed melting (CM), co-grinding (CG), kneading (KN) and solvent evaporation (SE) method. Based on the results of solubility of the SRT in SDs and DSC analysis, suitable method was selected for preparation of SRT-SD [11].

Preparation of Fast disintegrating tablets by direct compression method

FDTs of SRT-SD were prepared by direct compression using mucilage of *Plantago ovata as* natural superdisintegrant by direct compression method according to the formula given in **(Table 1)**. All ingredients shown in table 1 were co-ground in a pestle and motor and then magnesium stearate was added and mixed for 10 min. The mixed blend of drug-excipient was compressed using a single punch tablet machine to produce tablets of 8mm diameter [12]. The total weight of tablet is kept 200 mg.

Table 1: Composition of SRT-SD fast disintegrating tablets

Ingredients (mg/tab.) API/Excipients	F1	F2	F3	F4
SRT-SD	50	50	50	50
Plantago-ovata mucilage	2.5	5	7.5	10
Microcrystalline cellulose	60	60	60	60
Lactose monohydrate	85.5	83	80.5	78
Magnesium stearate	2	2	2	2
Total content	200	200	200	200

Pre-compression characterization

Bulk density

Bulk density of a compound varies well with the strategy of crystallization, edge or formulation. It is determined by pouring pre-sieved powder into a graduated cylinder via a large funnel and measure the volume and weight by following equation

$$\text{Bulk density} = \frac{\text{powder weight}}{\text{bulk volume}}$$

Tapped density

Tapped density is evaluated with machined for a permanent number of taps 10, 500 and 1250 till the powder bed volume have gone a least volume [13]. Tapped density can be computed by following equation

$$\text{Tapped density} = \frac{\text{powder weight}}{\text{tapped volume}}$$

Carr's index

Carr's index is measured using the values of bulk density and tapped density. The following equation is used to find the Carr's index;

$$CI = \frac{(Dt - Db)}{Dt} x100$$

Where, D_t = Tapped density and D_b = Bulk density

Hausner's ratio

The Hausner's ratio indicates the flowability and packing ability. When the Hausner's ratio is close to 1, materials have acceptable flow and packing ability [13]. Hausner's ratio was calculated using following equation

$$\text{Hausners ratio} = \frac{Dt}{Db}$$

Where, D_t = Tapped density and D_b = Bulk density

Post-compression characterization

Weight variation

20 core tablets of each trial were weighed on a calibrated balance and checked for weight variation and compared with acceptance criteria [14].

Hardness & thickness

The thickness and hardness of a tablet is the only dimensional variable related to the process. Hardness and

thickness of the tablets was evaluated by Erweka Hardness Tester

Disintegration time

DT of 6 core tablets of each trial was checked and compared with the limit mentioned in USP [14].

In-vitro dissolution studies

Dissolution studies of prepared SRT-SD fast disintegrating tablets were conducted at 5, 10, 15, 20, 30 and 45 min in sodium phosphate buffer P^H 6.8, 50 rpm and USP II apparatus (E). An aliquot (5ml) was withdrawn and replaced with fresh medium to maintain sink condition. Filtered samples were diluted appropriately and analyzed at 273nm by double beam UV visible spectrophotometer using dissolution medium as blank. The quantity of drug present within the samples was calculated by calibration curve constructed from reference standard. The comparison between RLD (Serta®) and formulated tablets was made so as to compare the drug release profile and physicochemical characteristics of drug product [13, 14].

Stability studies

The stability study was carried out on optimized formulation at 40°C/ 75% RH for three months as per ICH guidelines. The tablets were analyzed by dissolution study for it [15].

RESULTS AND DISCUSSION

Drug excipient compatibility studies

The physical examination of drug-excipient compatibility showed no change in the appearance of the drug with all the excipients in dry form as represented in **Table no.2** Thus all the selected excipients were compatible with the drug [16].

Table 2: Drug and excipient compatibility study

Sr. No.	Sample	Initial observation	After 40^0 C/ 75% RH (4 weeks)
1	SRT	White to off white powder	White to off white powder
2	SRT+ *Plantago ovata* seeds	White to off white powder	White to off white powder
3	SRT+ Lactose monohydrate	White to off white powder	White to off white powder
4	SRT+MCC	White to off white powder	White to off white powder
5	SRT+ Mg stearate	White to off white powder	White to off white powder

Phase solubility studies

Hydrophilic carrier used for the preparation of SD and its selection impacts in the solubility improvement of the poorly soluble drugs. The solubility of SRT was determined with different grades of HPMC (E3, E5 and E15) carrier. The solubility of SRT with carriers in aqueous solutions of 0.5, 1.0 and 1.5 % is illustrated in **Figure no.1** and the solubility parameters are presented in given **Table no.3**.The phase-solubility diagrams were organized based on the concentration of every carrier in water v/s the concentration of SRT. HPMC E5 showed the very best slope value, suggesting the most effective capability of the carrier to solubilise SRT. As compared to HPMC E15, the r^2 value obtained for HPMC E3 and HPMC E5 were on top of 0.99, demonstrating a positive impact on SRT solubility. The ΔGotr values indicate whether or not the reaction condition is unfavourable or favourable for the drug solubilisation in each carrier solution. All ΔGotr values were negative, indicating a good interaction and spontaneous SRT solubilisation. While, ΔGotr values for HPMC E3 weren't considerably bigger than that of E5, and, because of higher process and value effectiveness of HPMC E5, it absolutely was elect over HPMC E3 because the carrier for solid dispersion preparation. HPMC has been extensively used and reportable chemical compound for improvement in solubility of low soluble medication than alternative soluble carriers. The deliquescent polymer improves wettability of the drug by decreasing surface tension, rising wettability and solubility [17, 18]. Therefore it inhibits the re-crystallization of drug in dissolution medium.

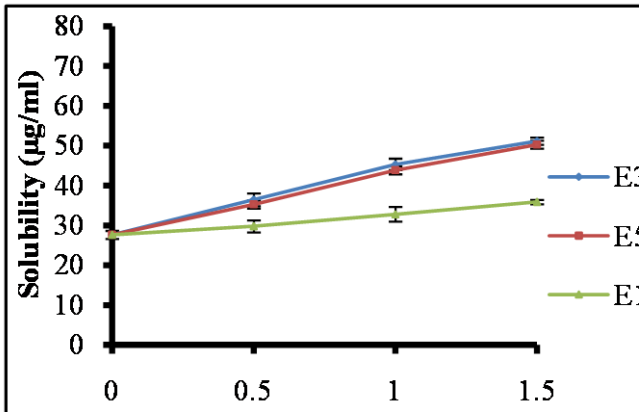

Figure 1: Phase solubility study

Table 3: Phase Solubility of SRT (µg/ml) at various grades of HPMC

Carrier Concentration (%w/v)	HPMC E3		HPMC E5		HPMC E15	
	Conc of SRT (µg/ml)	ΔG°_{tr} (kJ/mol)	Conc of SRT (µg/ml)	ΔG°_{tr}(kJ/mol)	Conc of SRT (µg/ml)	ΔG°_{tr}(kJ/mol)
0	27.6	-	27.6	-	27.6	-
0.5	37.42±1.59	-33.31	35.27	-50.97	29.74	-15.52
1	45.30 ±1.43	-103.00	43.84	-96.19	32.75	-35.56
1.5	51.12±1.72	-128.13	50.27	-124.64	35.84	-54.31
r^2	0.9834		0.9971		0.9532	
Slope	**15.88**		**15.31**		**5.55**	

Characterization of solid dispersion

Solubility of SRT in SDs

SRT-SD by various methods was prepared by taking drug/HPMC E5 in the molar concentrations of 1:1. The solubility of the SRT prepared by various methods is shown in **Figure no.2.** The solid dispersion prepared by SE showed maximum increase in aqueous solubility of SRT to 128.96±1.74 µg/ml (4.67 folds) while other methods *viz.* KN, CG and CM exhibited 109±1.60, 68.12±2.03 and 66.33±1.53 µg/ml improvement in solubility of SRT respectively. Greater enhancement in solubility of SDs by SE may be attributed to probable hydrogen bonds between HPMC and SRT formed due to solubilisation in a common solvent [19].

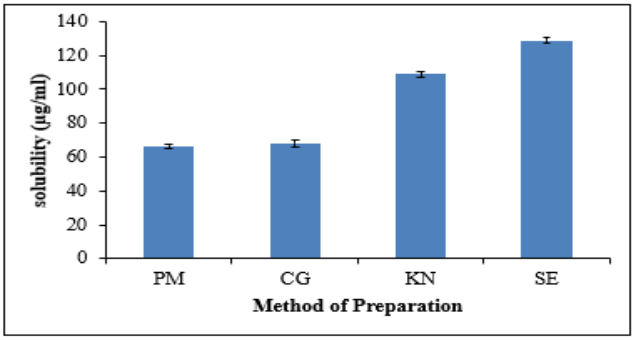

Figure 2: Solubility of SRT in SDs prepared by different methods

Where, **CM-** Closed Melting method, **CG-** Co-grinding method, **KN-** Kneading method, **SE-** Solvent evaporation method

Differential scanning calorimetry (DSC) analysis

Figure no.3 illustrates the DSC thermograms of SRT, HPMC E5 and SDs prepared by different methods. The thermogram of SRT shows a sharp endothermic peak at 250.73°C and in addition to another small endothermic peak at 218.5 °C which may be correlated to the polymorphic form V of SRT, indicating its crystalline nature and its melting point. The thermogram of HPMC E5 has not shown any distinct peaks while initial broad endothermic event may be attributed to moisture loss. SDs prepared by CM, CG and KN methods, the broadening of melting thermograms confirms the partial amorphisation of SRT. The disappeared melting peak of SRT in the SE endotherm confirms complete amorphisation could be due to the entrapment of SRT in the HPMC matrix [20]. This reflected a molecular dispersion of SRT in the HPMC E5. So SE (Solvent Evaporation) method was selected for preparation of SRT-SD.

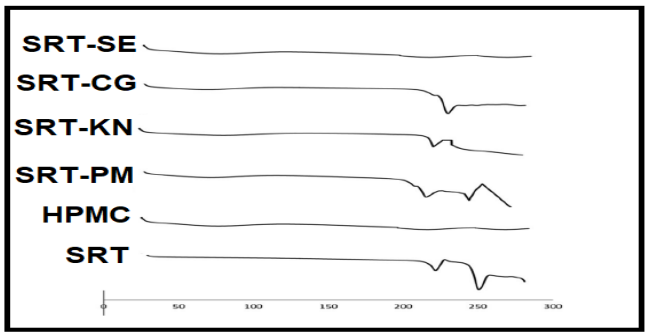

Figure 3: DSC thermograms of SRT and different SDs.

Pre-compression evaluation parameters

Micromeritic properties

Bulk density, tapped density, Carr's index and Hausner's ratio of all batches were checked and compared with USP limits. According to **Table no.4** micromeritic properties for granules of all batches were found to be having well to excellent flow properties.

Table 4: Micromeritic properties for SRT-SD granules

Tablet Batch	Bulk Density (g/ml)	Tapped Density (g/ml)	Carr's Index (%)	Hausner's ratio	Angle of Repose (degrees)
1	1 ± 0.11	1.14 ± 0.16	12.28 ± 1.25	1.14 ± 0.11	21.8 ± 2.41
2	0.96 ± 0.05	1.09 ± 0.15	11.84 ± 1.85	1.13 ± 0.09	21.3 ± 2.35
3	0.95 ± 0.1	1.05 ± 0.18	9.57 ± 1.02	1.1 ± 0.15	19.09 ± 1.54
4	1.02 ± 0.2	1.11 ± 0.099	8.14 ± 0.96	1.09 ± 0.07	18.43 ± 1.47

Post-compression evaluation parameters

Weight variation, hardness, friability, thickness and disintegration time

The tablets were examined for disintegration time, weight variation, hardness, thickness and friability. The results found satisfactory as compared to target parameters **(Table no.5)**

Table 5: Evaluation parameters of SRT-SD fast disintegrating tablets

Sr. No.	Average	Thickness	Hardness	Friability	Disintegration
1	201.3 ± 3.43	2.2 ±0.018	3.10 ±0.12	0.41	28 ± 2.9
2	194.7 ± 3.41	2.19 ± 0.017	4.5 ±0.19	0.3	16 ± 3.22
3	197 ± 3.68	2.23 ±0.011	4.2 ±0.12	0.33	10 ± 2.37
4	197.3 ± 3	2.21 ±0.015	3.89 ±0.08	0.39	9 ± 1.41

In-vitro dissolution studies

The dissolution study of SRT-SD tablets was carried out separately for each trial batch, according to USFDA recommended procedure and drug release profiles was calculated with reference to standard absorbance **(Figure no.4)** [21]. The batch with release kinetics closest to Serta® with maximum r^2 (0.9991) value was considered to be the optimized batch. F1 batch had a similarity factor of 57 (f2=57) when compared to Serta®. So F1 batch was considered as optimized batch which showed 95% drug release within 12 min.

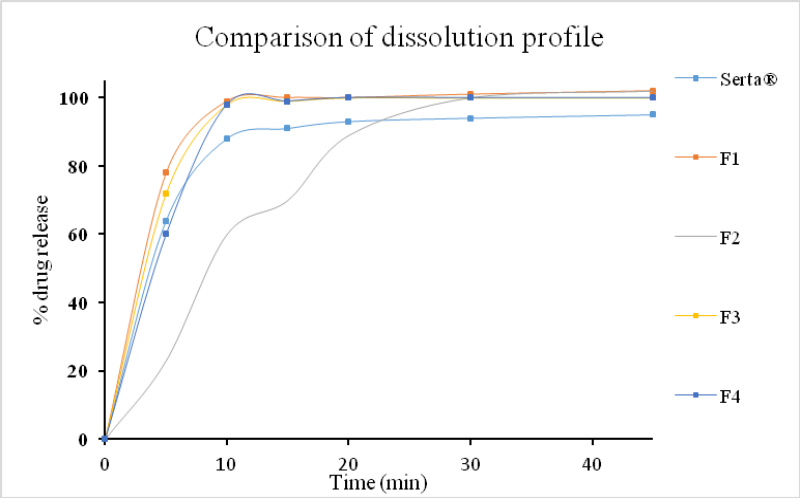

Figure 4: Comparison of in-vitro dissolution profile of SRT-SD tablets and Serta®

Stability Studies

The optimized batch F1 was subjected for stability storage condition for 03 month time period to study the impact of storage condition on dissolution profile. Drug release profiles were compared with the initial release. The stability study showed that there has been no sizable variation within the release profile of formulation **(Figure no.5)**, indicating no degradation of drug product.

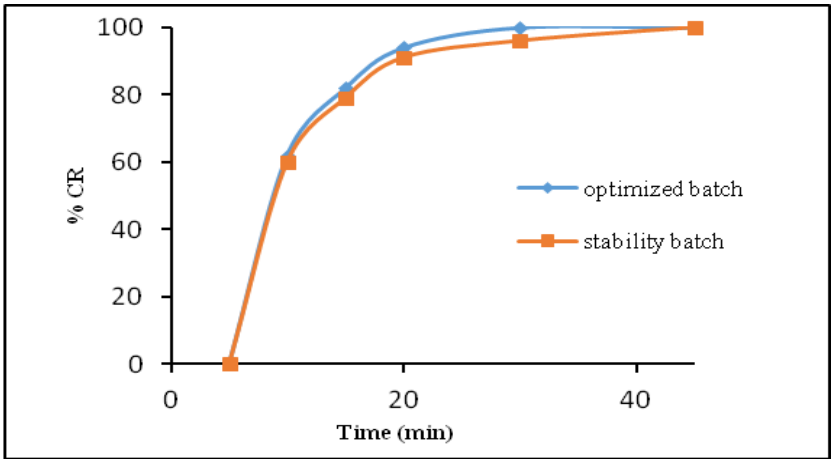

Figure 5: % cumulative release of SRT from optimized F1 batch and stability batch

CONCLUSION

The current study deals with the formulation development and *in-vitro* evaluation of SRT-SD fast disintegrating tablets. SRT used in the study was converted into SRT-SD using suitable method to improve its solubility. *Plantago ovata* mucilage showed effective application as natural superdisintegrant causing faster disintegration of tablets. The percent drug releases of the formulated batches were compared with marketed formulation Serta® which indicated F1 batch is optimized batch with similar release pattern as that of Serta®. Stability study was carried out and it showed that the release profiles of stability batch were comparable with initial batch and there was no noteworthy change in the rate and extent of the dissolution after the stability period. Thus, SRT-SD fast disintegrating tablets will be utilized as prominent drug delivery alternative for the treatment of depression.

CONFLICT OF INTEREST

The authors have no conflicts of interest regarding this investigation**.**

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