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FAST DISSOLVING TABLETS OF SERTRALINE HYDROCHLORIDE

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Abstract: Sertraline Hydrochlride, the selective serotonin reuptake inhibitor (SSRI) is widely used in treatment of depression. Though Sertraline Hydrochloride is well absorbed after oral dosing, there is a first pass metabolism leading to a reduced bioavailability of the drug (44%). Therefore, the present investigation is concerned with the development of Fast Dissolving Tablets of Sertraline Hydrochloride. Various formulations were prepared incorporating a combination of superdisintegrants (Physical Mixtures and Co-processed Mixtures), sodium starch glycolate, and crospovidone by direct compression method. The formulated Fast Dissolving Tablets were evaluated for various physicochemical parameters, disintegration time and for *in vitro* drug release. All the formulations had disintegration time less than 3 minutes and release maximum amount of drug by 5 min. Formulation containing Co-processed Mixtures had less disintegration time as compared to the Physical Mixtures. The most satisfactory formulatison was found to be stable during the stability studies conducted as per ICH guidelines QIC, as it showed no significant changes in the physicochemical properties, disintegration time.

Keywords: Fast Dissolving Tablet, Sertraline Hydrochloride, Sodium Starch Glycolate, Crospovidone, Direct Compression.

Introduction

It is always the aim of a scientist or a dosage form designer to enhance the safety of a drug molecule while maintaining its therapeutic efficacy. Recent advances in Novel Drug Delivery Systems (NDDS) aim for the same by formulating a dosage form, convenient to be administered so as to achieve better patient compliance. Pharmaceutical technologists have put in their best efforts to develop a Fast Dissolving Drug Delivery System. Tablets that disintegrate or dissolve rapidly in the patient's mouth are convenient for young children, the elderly and patients with swallowing difficulties, and in situations where potable liquids are not available. For these formulations, the small volume of saliva is usually sufficient to result in tablet disintegration in the oral cavity. The medication can then be absorbed partially or entirely into the systemic circulation from blood vessels in the sublingual mucosa, or it can be swallowed as a solution to be absorbed from the gastrointestinal tract. The sublingual route usually produces a faster onset of action than orally ingested tablets and the portion absorbed through the sublingual blood vessels bypasses the hepatic first-pass metabolic processes[1,2,3].

Sertraline Hydrochloride ((1*S*, 4S)-4-(3, 4-Dichlorophenyl)-1, 2, 3, 4 tetrahydro-*N*-methyl-1-naphthalenamine hydrochloride) is an antidepressant of the selective serotonin reuptake inhibitor (SSRI) class. The mechanism of action of Sertraline is presumed to be linked to its inhibition of CNS neuronal uptake of serotonin (5HT). Sertraline has been approved for the indications like Depression, Obsessive-compulsive disorder (OCD), Post-traumatic stress disorder (PTSD), Premenstrual dysphoric disorder (PMDD), Panic disorder (PD), Social phobia/social anxiety disorder, General anxiety disorder, Binge eating disorder, Premature ejaculation. Sertraline undergoes extensive first pass metabolism and having oral availability of 44%, thus suitable candidate for Fast Dissolving Systems.

Co-processing is the one of the most widely explored and commercially utilized method for the preparation of directly compressible adjuvants. Co-processing defined as combining two or more established excipients by an appropriate process. Co-processing of excipients could lead to the formation of excipients with superior properties compared to the simple physical mixtures of their components. The main aim of co-processing is to obtain a product with added value related to the ratio of its functionality/price. Development of co-processed directly compressible adjuvant starts with the selection of the excipients to be combined, their targeted proportion, selection of preparation method to get optimized product with desired physico-chemical parameters and it ends with minimizing avoidance with batch-to-batch variations. In the present study, various Fast dissolving

Tablets formulations of Sertraline Hydrochloride were prepared using physical mixture of superdisintegrants and Co-processed superdisintegrants. Sodium Starch Glycollate and Crospovidone were used in different ratios as superdisintegrants for Co-processing. The fast disintegrating tablets were prepared by direct compression of Co-processed superdisintegrants with sertraline hydrochloride[4,5].

Materials and Methods

Sertraline hydrochloride was obtained as a gift sample from Unichem Baddi. Sodium Starch Glycollate and Crospovidone were obtained as gift samples from Signet, Mumbai.

Preparation of Physical Mixtures

Physical mixtures were prepared in ratios from 1:1, 1:2, 1:3 with the help of mortar and pestle. (Table 1)

Preparation of Co-processed Mixtures

Various blends of crospovidone and SSG having total weight of 10g were prepared in ratios from 1:1, 1:2, 1:3 and was added to 65 mL of isopropyl alcohol. The contents of the beaker (250 mL capacity) were stirred on a magnetic stirrer. The temperature was maintained between 65ºC and 70ºC, and stirring was continued till most of isopropyl alcohol evaporated. The wet coherent mass was granulated through 60-mesh sieve. The wet granules were dried in a tray dryer at 60ºC for 20 minutes. The dried granules were sifted on 60-mesh sieve and stored in airtight container till further use (Table 1).

Formulation of Fast Dissolving Tablets

Fast dissolving tablets of Sertraline HCl were prepared by using direct compression method after incorporating physical mixtures and coprocessed mixtures of superdisintegrants (2.5%). Ten formulations of Sertraline Hydrochloride were prepared. Tablet weight was 300 mg; 11 mm punch was used for compression by using Cadmach single Punch Machine. Ingredients are depicted in Table 2.

Evaluation of Tablets

Prepared tablets were evaluated for post compression parameters like thickness, hardness, weight variation, friability test, drug content uniformity, taste evaluation, wetting time, *in vivo* dispersion, *in vivo* disintegration time, and stability studies.

General Appearance, Thickness, Hardness Test[6]

Five tablets from both batches were randomly selected and organoleptic properties such as color, odor, taste, shape, were evaluated. The thickness of five tablets was measured using vernier calipers. The diameter was also determined by using vernier calipers. Hardness of the tablets was tested by using 'Monsanto' hardness tester (Table 3 and Table 4).

Weight uniformity[7]

The standard pharmacopoeial procedures were followed for this purpose. According to USP, 20 tablets were randomly selected and individually as well as collectively weighed on a digital balance. Then percentage deviation from the average was calculated (Table 3 and Table 4).

Uniformity of Content[8]

10 tablets were randomly selected and weighed. Average weight was calculated. Tablets were powdered in a glass mortar. Powder equivalent to 50 mg was weighed and the weighed amount was dissolved in 50 ml of methanol in different volumetric flasks to obtain a stock solution of 1000 µg/ml. 1 ml was pipetted out and diluted with methanol to 10 ml in each case, so as to get 100 µg/ml solutions. The absorbance was noted down after filtering off the solutions at 266 nm. The average weight of drug present in each tablet was calculated and compared with the claimed amount. The tablets complied with the test if not more than one of the individual values thus obtained is outside the limit 85 to 115% of the average value (Table 3 and Table 4).

Friability[9]

Friability of the tablets was determined using Roche friabilator. This device subjects the tablets to the combined effect of abrasions and shock in a plastic chamber revolving at 25 rpm and dropping the tablets at a height of 6 inch in each revolution. Preweighed sample of tablets was placed in the friabilator and were subjected to 100 revolutions. Tablets were de dusted using a soft muslin cloth and reweighed.

The friability (F%) is given by the formula

$$F\% = \left(1 - \frac{Wo}{W}\right) X100$$

Where, W_0 is weight of the tablets before the test and W is the weight of the tablets after test (Table 3 and Table 4).

Wetting time[10]

A piece of tissue paper folded twice was placed in a small petridish (internal diameter = 6.5 cm) containing 6 ml of simulated saliva pH (phosphate buffer pH 6.8). A tablet was put on the paper, and the time required for complete wetting was measured. Six trials for each batch were performed; average time for wetting with standard deviation was recorded (Table 3 and Table 4).

***In vitro* disintegration time[11]**

In vitro disintegration time was performed by apparatus specified in USP. Phosphate buffer pH 6.8, 900 ml was used as disintegration medium, and the temperature of which maintained at 37 ± 2°C and the time in second taken for complete disintegration of the tablet with no palpable mass remaining in the apparatus was measured in seconds (Table 3 and Table 4).

***In Vitro* Dispersion Test[12]**

This test is performed to ensure disintegration of tablets in the salivary fluid, if it is to be used as a fast dissolving tablet. *In vitro* dispersion time was measured by dropping a tablet in a measuring cylinder containing 6 ml of simulated salivary fluid of pH 6.8. Five tablets from each formulation were randomly selected and *in vitro* dispersion time was performed. (Preparation of simulated salivary fluid: Phospate buffer pH 6.8 mimics the salivary fluid. Dissolve 13.872 g of potassium dihydrogen phosphate and 35.084 g of disodium hydrogen phosphate in sufficient water to produce 1000 ml).

***In Vitro* Dissolution Studies**

In vitro dissolution studies for all the fabricated tablets was carried out using USP paddle method at 50 rpm in 900 ml of phosphate buffer (pH 6.8) as dissolution media, maintained at 37±0.5°C. 5 ml aliquot was withdrawn at the specified time intervals, filtered through whatmann filter paper and assayed spectorphotometrically at 266 nm. An equal volume of fresh medium, which was prewarmed at 37°C was replaced into the dissolution media after each sampling to maintain the constant volume throughout the test (Fig 1).

Stability Studies

Stability studies were carried out to ensure the quality and safety of the formulations. The formulations were kept under different storage conditions for a period of 2 months. The following storage conditions were provided to study the stability characteristics of the tablets. The conditions complied with the ICH guidelines:

1. 40º Temperature
2. 50º Temperature
3. 60º Temperature
4. 37º ± 75% RH

The tablets were packed in suitable containers and kept under the above mentioned storage conditions. The effects of temperature and time on the physical characteristics of the tablet were evaluated for assessing the stability of the prepared formulations. The different parameters that were studied are disintegration time, hardness, drug content.

Result and Discussion

In the present study, Sertraline Hydrochloride were prepared by using physical and Co-processed mixtures sodium starch glycolate, and crospovidone as superdisintegrants. A total number of ten formulations were prepared by direct compression technique. The values of pre-compression parameters evaluated were within prescribed limits and
indicated good free flowing property. IR spectroscopy was used as means of studying drug-excipient compatibility and confirmed undisturbed structure of Sertraline Hydrochloride, which indicates no drug-excipient interaction. The data obtained of postcompression parameters such as hardness, friability, weight variation, uniformity of content, thickness, wetting time, disintegration time are shown in Table 3 and Table 4. The hardness was found to be in the range of 3 to 3.4 kg/cm^2 in all the formulations indicating good mechanical strength with an ability to withstand physical and mechanical stress conditions while handling. The values of thickness were found to be in the range of 4.316 to 4.336. In all the formulations the friability value is less than 1% and meets the IP (Indian Pharmacopoeia) limits[13]. All the tablets passed weight variation test as the % weight variation was within the pharmacopoeial limits[13].The weight of all the tablets was found to be uniform with low standard deviation values indicating efficient mixing of drug, superdisintegrants and excipients. The percentage drug content of all the tablets was found to be between 96.32 % and 101.8 of Sertraline Hydrochloride, Table 1 and Table 2 which was within the acceptable limits. The percentage drug release by each tablet in the *in vitro* drug release studies were based on the mean content of the drug present in respective tablet. The result of disintegration, wetiing and dispersion studies shows that the formulation F_{10} took the shortest disintegration time however all the formulations took lesser disintegration time as required that is 3 minutes. The result of *in vitro* disintegration of all the tablets were found to be within prescribed limit and satisfy the criteria of FDT. Overall the FDT formulations of haloperidol showed an average of 81.96 to 97.56% drug release range at the end of 10 min and it was also observed that formulations F_{10} took shortest time to release the maximum amount of drug whereas the other formulations took more than 10 min to release the drug. From both pre and post formulations parameters, a comparative study was performed in between tablets formed by co-processed mixtures and physical mixtures of superdisintegrants. It was found that the tablets prepared by co-processed mixtures had given the better results as compared to those prepared by physical mixtures.

Table 1 Different Blend Formulations

Code of Mixture	PM1 CP1	PM2 CP2	PM3 CP3	PM4 CP4	PM5 CP5
SSG	1	2	3	1	1
Crospovidone	1	1	1	2	3

Table 2: Different FDT Formulations

Ingredients	Formulation code									
	F_1	F_2	F_3	F_4	F_5	F_6	F_7	F_8	F_9	F_{10}
Dibasic calcium Phosphate	**75**	**75**	**75**	**75**	**75**	**75**	**75**	**75**	**75**	**75**
Dextrose	**25**	**25**	**25**	**25**	**25**	**25**	**25**	**25**	**25**	**25**
Talc	**6**	**6**	**6**	**6**	**6**	**6**	**6**	**6**	**6**	**6**
Magnesium Stearate	**6**	**6**	**6**	**6**	**6**	**6**	**6**	**6**	**6**	**6**
MCC	**180.5**	**180.5**	**180.5**	**180.5**	**180.5**	**180.5**	**180.5**	**180.5**	**180.5**	**180.5**
PM1	**7.5**									
PM2		**7.5**								
PM3			**7.5**							
PM4				**7.5**						
PM5					**7.5**					
CP1						**7.5**				
CP2							**7.5**			
CP3								**7.5**		
CP4									**7.5**	
CP5										**7.5**
TOTAL	**300**	**300**	**300**	**300**	**300**	**300**	**300**	**300**	**300**	**300**

Table 3 Different Evaluation Parameters From Formulations F_1-F_5

Evaluation Parameter	Formulation code				
	F_1	F_2	F_3	F_4	F_5
Bulk Density (g/cm^3)	0.668±0.031	0.613±0.016	0.669±0.024	0.608±0.041	0.665±0.021
Tapped Density (g/cm^3)	0.754±0.010	0.702±0.011	0.757±0.025	0.682±0.050	0.756±0.018
Hausner's Ratio	1.129±0.038	1.146±0.025	1.131±0.015	1.121±0.015	1.136±0.019
Compressibilty Index(%)	11.362±2.985	12.738±1.958	11.599±1.213	10.809±1.259	11.997±1.487
Angle of Repose(^{0})	24.20±1.379	23.408±1.131	24.789±0.911	24.216±1.247	24.898±0.718
Hardness (kg/cm^3)	3.1±0.152	3.2±0.113	3.4±0.165	3.1±0.123	3.3±0.165
Friability (%)	0.73±0.039	0.80±0.049	0.81±0.059	0.93±0.034	0.96±0.072
Weight (mg)	301.4±4.921	303.6±4.311	302.1±1.932	304.2±4.974	303.1±4.216
Thickness (mm)	4.336±0.031	4.316±0.017	4.319±0.038	4.321±0.026	4.328±0.012
Drug Content (%)	101.08	99.32	96.32	99.57	97.73
Wetting Time (sec)	108.24±2.27	92.25±2.5	88.14±3.41	90.4±3.62	79.43±4.37
***In vitro* Disinteration Time (sec)**	130.24±2.35	116.34±2.45	106.33±3.31	113.24±1.24	98.74±1.65
***In vitro* Dispersion Time (sec)**	142.1±2.33	132.4±2.55	123.3±2.4	128.1±2.34	119.1±5.21

Table 4 Different Evaluation Parameters From Formulations F_6-F_{10}

Evaluation Parameter	Formulation code				
	F_6	F_7	F_8	F_9	F_{10}
Bulk Density (g/cm^3)	0.670±0.046	0.661±0.019	0.660±0.018	0.611±0.042	0.607±0.021
Tapped Density (g/cm^3)	0.755±0.033	0.746±0.042	0.728±0.025	0.691±0.064	.678±0.018
Hausner's Ratio	1.130±0.019	1.128±0.028	1.103±0.012	1.130±0.019	1.116±0.032
Compressibilty Index(%)	11.258±2.985	11.394±1.657	9.340±1.543	11.577±1.242	10.471±1.727
Angle of Repose(^{0})	26.347±1.087	24.973±1.187	24.789±0.911	22.586±1.187	21.713±0.754
Hardness (kg/cm^3)	3.1±0.246	3.3±0.122	3.2±0.128	3.1±0.291	3.0±0.231
Friability (%)	0.63±0.176	0.69±0.171	0.57±0.139	0.41±0.164	0.41±0.164
Weight (mg)	301.7±3.913	302.4±2.814	299.3±2.765	303.8±4.131	299.7±2.721
Thickness (mm)	4.312±0.041	4.316±0.017	4.319±0.038	4.321±0.026	4.328±0.012
Drug Content (%)	99.48	99.65	100.17	98.78	98.52
Wetting Time (sec)	79.43±4.37	65.37±3.9	49.14±3.12	60.8±3.92	44.42±3.63
In vitro Disinteration Time (sec)	98.74±1.65	86.37±3.96	67.33±4.01	81.36±3.41	59.82±3.18
In vitro Dispersion Time (sec)	119.1±5.21	107.6±2.39	87.5±4.15	103.2±2.71	72.3±4.13

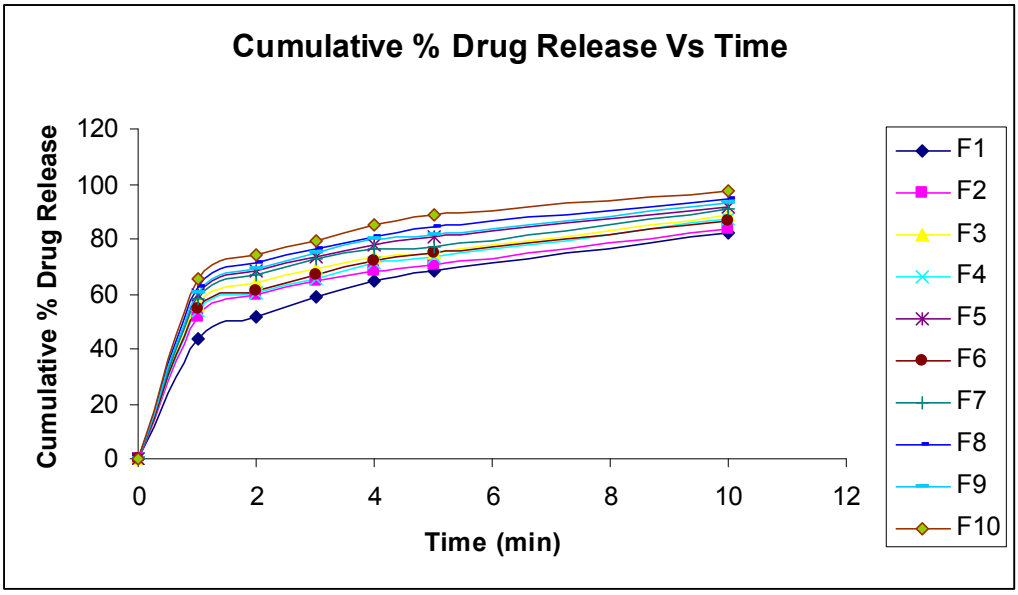

Fig 1 *In vitro* Dissolution Profile of Prepared Formulations

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