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Research Article

SOLUBILITY ENHANCEMENT AND FORMULATION OF FAST DISSOLVING TABLET OF ZIPRASIDONE HYDROCHLORIDE

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ABSTRACT

The use of Fast dissolving tablet provide an advantage particularly for pediatric and gediatric populations who have difficulty in swallowing conventional tablets and capsules. Ziprasidone Hydrochloride, a BCS class II drug is an atypical antipsychotic agent for the treatment of schizophrenia and mania. It exhibit poor solubility problem. The present work was aimed at overcoming this limitation. Drug-Hydroxypropyl-β-Cyclodextrin and sulfobutylether-β-Cyclodextrin complex were prepared and characterized by FTIR, DSC and Saturated solubility studies. The inclusion complexes with Sulfobutylether-β-cyclodextrin showed higher solubility and it was incorporated into Fast dissolving tablet. Nine types of different formulas of 20 mg Ziprasidone Hydrochloride were prepared by direct compression method; synthetic superdisintegrants like sodium starch glycolate and crosspovidone achieve rapid disintegration was selected for the preparation of Fast dissolving tablet. Tablets were evaluated for the hardness, friability, thickness, disintegration time, weight variation and drug release study.

Keywords: Ziprasidone Hydrochloride, Fast dissolving tablet, Solid dispersion

INTRODUCTION

Drug solubility is one of the most important physicochemical property. The bioavailability of an orally administered drug depends on solubility in gastrointestinal tract and permeability across cell membrane.Hence, two areas of pharmaceutical research that focus on improving the bioavailability of active agent include:

i. Enhancing solubility and dissolution rate of poorly water soluble drugs and
ii. Enhancing permeability of poorly permeable drug[1]

Solid dispersions offer a variety of processing and excipient options that allow for flexibility when formulating oral delivery systems for poorly water soluble drugs.[1] Cyclodextrin Complexation process has been emerged as effective tool to increase solubility of poorly soluble drugs.[2,3]Fast dissolving tablet is a solid dosage form containing medicinal substance or active ingredient which disintegrate rapidly usually within a matter of seconds when placed on a tongue.[4,5]It has following advantages:[6]

- Administration to the patients who cannot swallow, such as the elderly, stroke victims, bedridden patients and patients who refuse to swallow such as pediatrics, gediatric and psychiatric patients.
- Achieve increased bioavailability/rapid absorption through Pregastric absorption of drugs from mouth, pharynx and esophagus as saliva passes down.
- Convenient for administration and patient compliant.

Schizophrenia is a devastating disorder of the mind and brain. Ziprasidone Hydrochloride is a new atypical antipsychotic, proved to be effective in the treatment of schizophrenia. Chemically it is 5-{2-[4-(1,2-benzisothiazole-3-yl)-1-piperzinyl]ethyl}-6-chloro,1,3-dihydro-2H-indole-2-one.[7] Ziprasidone Hydrochloride is rapidly absorbed and extensively metabolized by N-dealkylation, oxidation, reductive cleavage, hydration and N-dearylation. It have affinity for adrenergic, histamine, serotonin and

dopamine receptors.[8] Ziprasidone Hydrochloride is a poorly soluble drug. The goal of this study is to increase the solubility of drug by preparing solid dispersions with different polymers and formulate it into Fast dissolving tablet.

MATERIAL AND METHODS

MATERIALS

Ziprasidone Hydrochloride was a gift sample from Macleoids Pharmaceutical Ltd, Mumbai. Sulfobutylether-β-cyclodextrin, Hydroxypropyl-β-cyclodextrinwere obtained from Glenmark Pharmaceuticals, Sinnar, Nashik. Crosspovidone, Sodium starch glycolate, magnesium stearate, talc and Microcrystalline cellulose were obtained from Modern Science Pvt. Ltd, Nashik.

METHODS

Pre-formulation study

UV spectroscopy

The drug was scanned in UV Spectrophotometer to detect the λmax and to drawn the calibration curve of the drug in Methanol as a solvent. The drug was used in concentration ranges of 5-30 ppm. The spectra and calibration curve of the drug is as shown in **Figure 1 and 2**.

FT-IR spectrum

The drug was subjected to FT-IR studies (Shimadzu; 8400S) for the purpose of characterization. FT-IR technique is one the most powerful technique of chemical identification. Samples were prepared by KBr disc method (2 mg sample in 100 mg KBr) and examined in the transmission mode. Each spectrum was measured over a frequency range of 4000–400 cm−1.The spectra shown in **Figure 3, 4, 5, 6**.

Differential scanning calorimetry (DSC)

Thermogram of Ziprasidone Hydrochloride was obtained using differential scanning calorimetry. Sample was kept in aluminium pan, sealed and heated at constant rate of 10°C/min over temperature range of 10 to 200°C. By purging nitrogen with flow rate of 10 mL/min inert atmosphere was maintained. The results are shown in **Figure 7, 8**.

Preparation of Inclusion Complex of Ziprasidone Hydrochloride by Kneading Method

Drug and Hydroxypropyl-β-Cyclodextrin and Sulfobutylether-β-cyclodextrin in the proportion of appropriate molar ratio were mixed in a mortar for one hour with small quantities of methanol was added intermittently to get slurry like consistency. The paste was dried in the oven at the temperature of 45˚C. Dried complex were pulverized into fine powder and sifted with sieve # 80.

Saturation Solubility Study

Saturation solubility studies were carried out for all inclusion complexes prepared. This study was the basic criteria to identify and judge a inclusion complex of choice, which would enhance the solubility and so, would show good results in *in-vitro* dissolution studies. Solubility studies were carried out in glass vials. In each of these vials, 10 ml distilled water was added. Excess quantities of inclusion complex were added into each of vials. These vials were shaken continuously for 24 hours on a lab shaker and the resulting solutions were filtered, appropriate dilutions were made and UV absorbances were recorded at 317 nm.

Method of preparation of powder blend

Inclusion complex of ZPS: Sulfobutylether-β-cyclodextrin (containing 300 mg of inclusion complex which is equivalent to 20 mg of ZPS) and other inactive ingredients along with varying % of SSG and Crosspovidone mentioned in table 1. For this a 3^2 factorial design was applied using two superdisintegrants (SSG and Crosspovidone) at three concentration levels. Formulations coded as F1 to F9 respectively. In the first step, active and inactive ingredients weighed accurately and were screened through a 60-mesh sieve. The inclusion complex (ZPS: Sulfobutylether-β-cyclodextrin) and superdisintegrants were blended first in mortar and pestle then the remaining ingredients were added in that and blended for 20 min. Finally the blend is passed through mesh #40 and used for evaluation of flow characteristic. Formula for Fast Dissolving tablet of Ziprasidone Hydrochloride is shown in **Table 1**.

Evaluation parameters

Evaluation of pre compression parameters of the powder blends

Pre-compression parameters of the prepared blend of all the formulations were studied by determining the Bulk density, Tapped density, Compressibility index, Hausner's ratio and Angle of repose. The results are shown in **Table 2**.

Evaluation of post compression parameters of the powder tablets

The compressed Fast dissolving Ziprasidone Hydrochloride tablets were subjected to

various physical tests which include hardness, friability, weight variation, thickness and drugs content uniformity. The results are shown in **Table 3**.

Hardness test
For each formulation, the hardness of three tablets was checked using the Monsanto hardness tester (LAB- HOSP) average values are shown in **Table 3**.

Thickness
The thickness of tablet is important for uniformity of tablet size. The thickness of the tablets was determined using a Vernier Calliper. Three tablets from each batch were used and average values are shown in **Table 3**.

Friability
Friability is the measure of tablet strength. In this test, number of tablets subjected to combined effect of shock abrasion by utilizing a plastic chamber which revolves at a speed of 25rpm, dropping the tablets at a distance of 6 inches in each revolution. A sample of pre-weighed tablets was placed in Roche Friability tester (Kumar Mfg. Ltd.) This was then operated for 100 revolutions. The tablets then dedusted and reweighed. Permitted friability limit is 1.0%. Tablets were then weighed and friability values were determined and are reported in **Table 3**.

Weight variation
Twenty tablets were weighed individually. Average weight was calculated from the total weight of all tablets. The individual weights were compared with the average weight. The percentage difference in the weight variation should be within the acceptable limits (±7.5%). The results are shown in **Table 3**.

Drug Content Uniformity Study
Five tablets were weighed individually and powdered. The powder equivalent to 20 mg of Ziprasidone Hydrochloride was weighed and dissolved in 20 ml of Methanol. The volume was made to 100ml with Methanol. From this stock solution, 20 µg/ml dilutions were prepared. The drug contents of the resulting solution were calculated from UV absorbance at 317 nm. The results are shown in **Table 3**.

Disintegration time study
The *in-vitro* disintegration studies were carried out using Tablet Disintegration Test Apparatus. One tablet was placed in each of the six tubes of the basket assembly and disk was added to each tube. This assembly was then suspended in one-liter beaker containing water maintained at 37±2^{0}C. The basket was then moved up and down through a distance of 5 to 6 cm at a frequency of 28 to 32 cycles per minutes. The time required for complete disintegration of the tablet was recorded. The test was performed for tablets of all type of formulation (F1-F9). The results are shown in **Table 3**.

***In - vitro* Drug Release Study**
An *in-vitro* drug release studies of the prepared nine formulations of Fast dissolving tablets were conducted for a period of 20 minutes using an eight station USP type 2 apparatus (paddle type)(Electrolab).The agitation speed was 50 rpm. Prepared Fast dissolving tablets were added to 900 ml Phosphate buffer 7.4 at 37 ± 0.5° C and stirred at 50 rpm. 5 ml aliquots were withdrawn at time intervals of 2,4,6,8,10,12,14,16,18,20 min. and filtered through Whatmans No. 41 filter paper. An equal volume of fresh dissolution medium was replaced to maintain the volume of dissolution medium. The filtered samples were analyzed. Cumulative percentage of labeled amount of drug released was calculated.The results are shown in **Table 4**.

RESULT AND DISCUSSION
The prepared Fast dissolving tablets were evaluated for thickness, weight variation, hardness, friability, drug content, disintegration time and *in-vitro* drug dissolution studies. All the studies were performed in triplicate, and results are expressed as mean ± SD.

Drug and Excipients Compatibility Studies
UV Spectroscopy
The λmax of Ziprasidone Hydrochloride was obtained at 317.4nm and the calibration curve was constructed using concentration range 5-30 ppm, and the regression coefficient R^2 = 0.999. Spectra and calibration curve showed in **Figure 1,2.**

FTIR spectral studies
FTIR spectra of pure Ziprasidone Hydrochloride and excipients are shown in **Figures 3, 4, 5, 6.** The FTIR spectrum of Ziprasidone Hydrochloride showed Stretching vibrations at 1381 cm^{-1} for C-N bond, 743 cm^{-1} for C-Cl bond, 3412 cm^{-1} for N-H bond and 3149 cm^{-1} for C-H (aromatic) bond. All these characteristic bands were all retained in formulations indicating that there is no interaction between drug and polymers.

DSC analysis

DSC Thermograms of Ziprasidone Hydrochloride and Formulation were shown in **Figures 7, 8**.Ziprasidone Hydrochloride showed sharp endothermic peak at 235.84°C corresponding to its melting point. Ziprasidone Hydrochloride formulations showed peak at 240.43°COverall DSC curves indicate that there is no interaction observed between drug and excipients.

Pre compressional parameters

The powder blends was prepared by mixing of various ingredients mentioned in **Table 1**and used for characterization of various flow properties of powder. **Table 2**reports the values for Compressibility Index (CI) and Hausner's ratio (HR) for all prepared batches. According to the literature, powders with CI values between 9% -13% are suitable for producing the tablets and those with a Hausner's ratio values below 1.25 and angle of repose values in between 20-40˚ indicate good flow properties of powders.

Post compressional parameters

The present work undertaken to formulate and evaluated fast dissolving tablet of Ziprasidone Hydrochloride by direct compression method. Superdisintegrants at different concentration levels were included to assist fast disintegration.The results are shown in **Table 3**.

Disintegration time

Fast dissolving tablet of Ziprasidone Hydrochloride should disintegrate within minute. Three Tablets of each formulation were taken and placed in 6 tubes of disintegration apparatus. The time taken for complete disintegration was noted.The disintegration time for formulation F1-F9 was found to be in the range of 38 to 54 sec, this reflects that the optimum concentration of superdisintegrants, rapid will be disintegration, Formulation F7 containing high percentage of sodium starch glycolate and crosspovidone showed more disintegration time among the F1-F7 formulation.

In-*vitro* dissolution studies

In –vitro dissolution studies were carried out in 900ml of phosphate buffer 7.4 as dissolution medium using US type II (paddle method) dissolution rate test apparatus (Electrolab) at 50 rpm for 20 min. The temperature was maintained constant at 37±0.5^{0}C. The dissolution experiments were conducted in triplicate. In-Vitro release study was shown 98.38%release of Ziprasidone hydrochloride through F7 formulation in 20 min. By observing results the F7 batch was selected as optimized formulation.

CONCLUSION

Ziprasidone Hydrochloride is very slightly soluble in water. Oral bioavailability of Ziprasidone Hydrochloride can be improved by using the technique of Inclusion complex formation. Inclusion complex of Ziprasidone Hydrochloride done by kneading method and for this selected carrier is Sulfobutylether-β-cyclodextrin.The prepared ratios of inclusion complexes were characterized by FT-IR, DSC,Saturation solubility. Based on the results of saturation solubility studies the inclusion complex of ZiprasidoneHydochloride with SBE-β-CD with ratio 1:3 indicates highest increase in solubilitywas selected as optimized combination for Ziprasidone Hydrochloride. The inclusion complex prepared by different ratios of drug to carrier showed solubility enhancement in the order of 1:3 > 1:2 > 1:1.The optimized combination was formulated into Fast dissolving tablet. Fast dissolving tablet prepared by using superdisintegrant like SSG and Crosspovidone. The effect of types and concentrations of superdisintegrant on the disintegration time and dissolution profile of Ziprasidone Hydrochloride fast dissolving tablets were studied. The % drug release of Fast Dissolving tablet F7 shows 98.25 % drug release after 20 minutes. However further *in vivo* studies are needed to justify the effect of increasing solubility of Ziprasidone Hydrochloride on its bioavailability.

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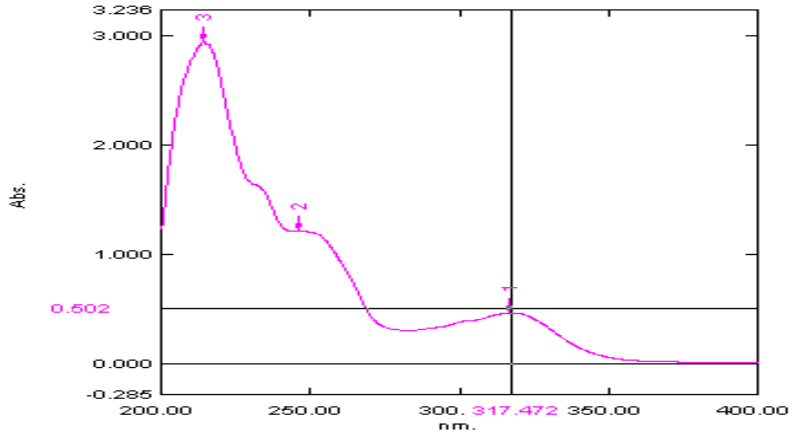

Fig. 1: UV Spectrum of Ziprasidone Hydrochloride in Methanol

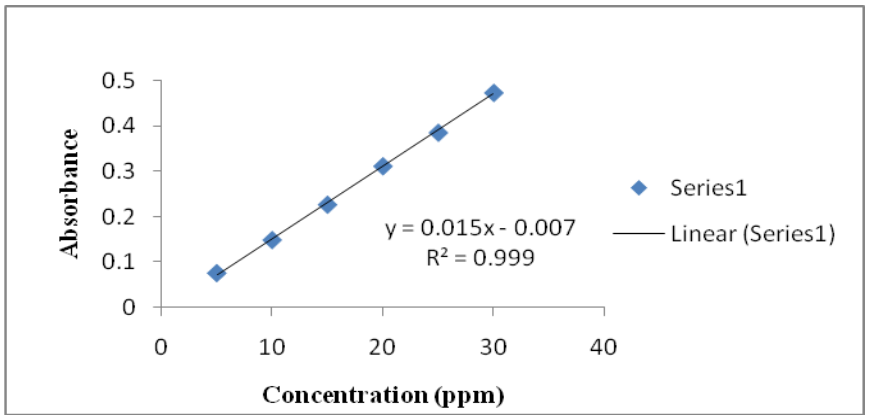

Fig. 2: Calibration Curve of Ziprasidone Hydrochloride in Methanol

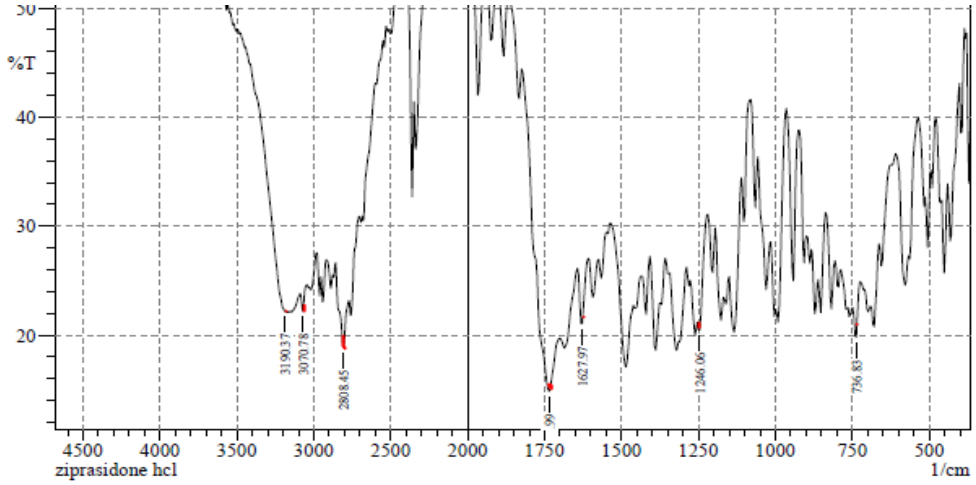

Fig. 3: FT-IR Spectrum of Ziprasidone Hydrochloride

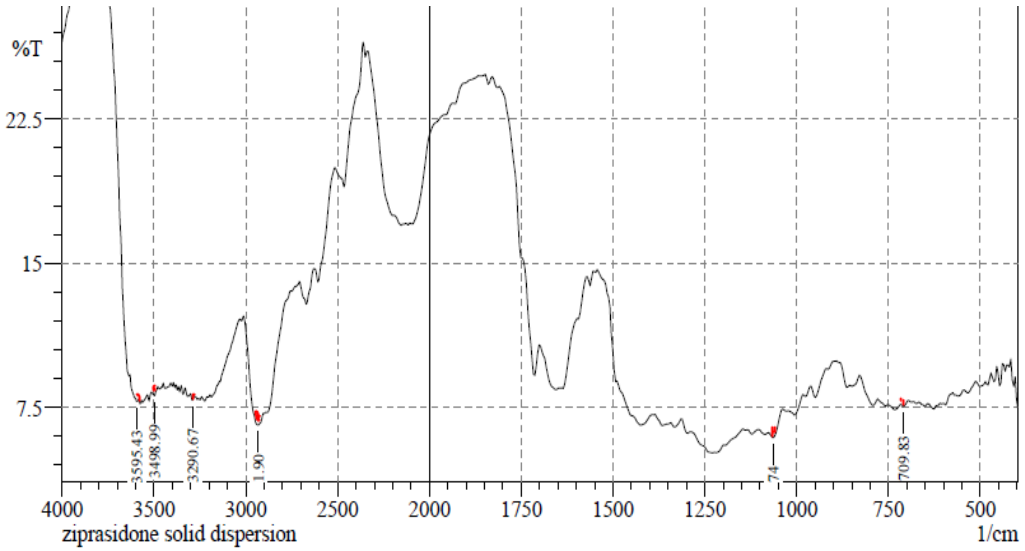

Fig. 4: FT-IR. Spectrum of ZPS:SBE-β-CD Inclusion Complex

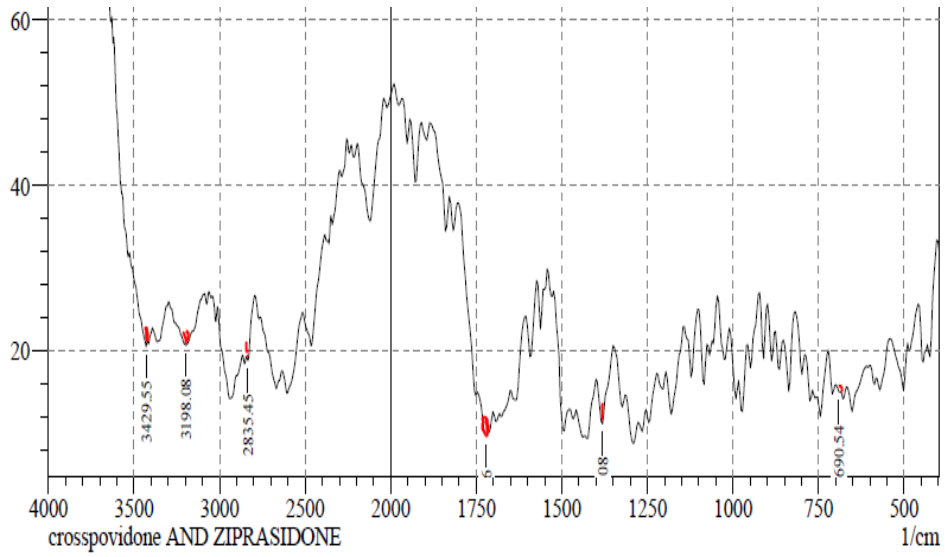

Fig. 5: FT-IR study of drug and crosspovidone

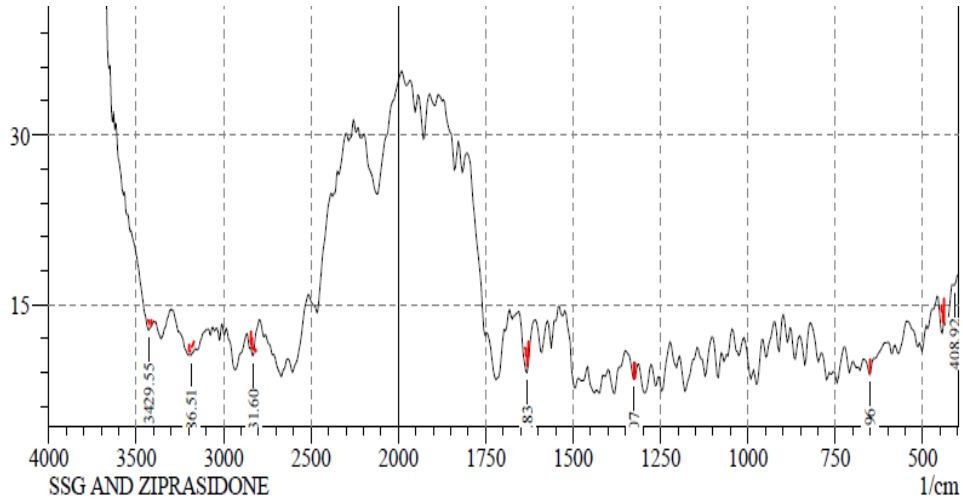

Fig. 6: FT-IR study of drug and SSG

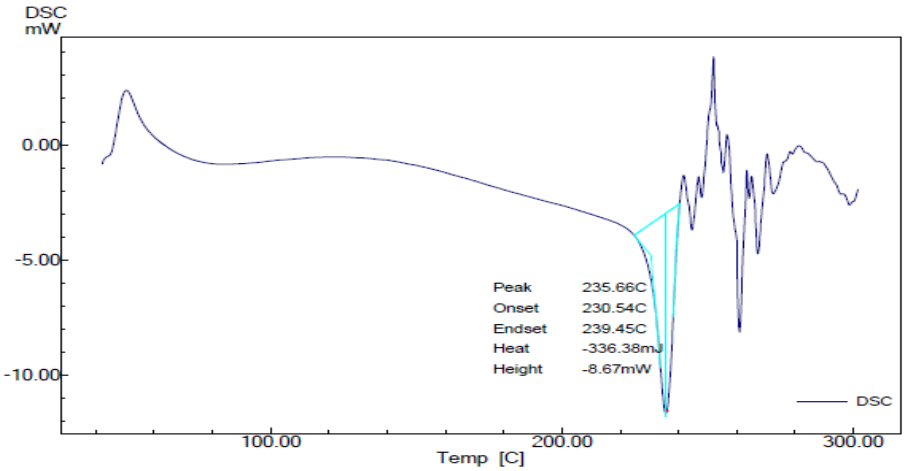

Fig. 7: DSC of Ziprasidone Hydrochloride

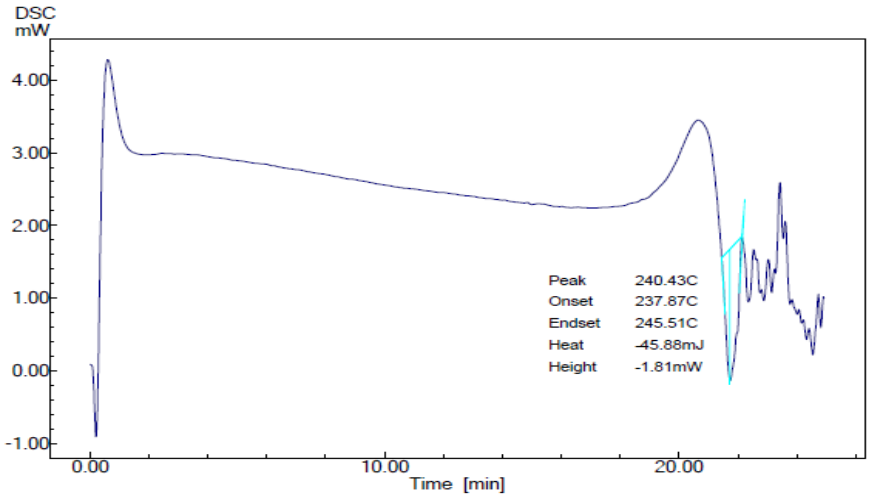

Fig. 8: DSC of Ziprasidone Hydrochlorideformulation

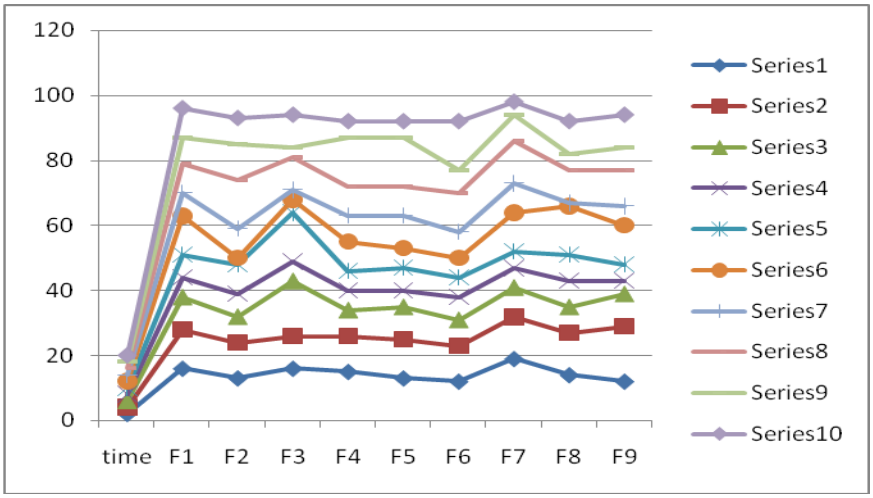

Fig. 9: Comparative *In-vitro* drug release profile

Table 1: Formula for Fast Dissolving tablet of Ziprasidone Hydrochloride

Sr. No.	Ingredients (mg)	Formulations								
		F_1	F_2	F_3	F_4	F_5	F_6	F_7	F_8	F_9
1.	Amount of Drug and SBE-β-CD complex(1:3) equivalent to 25mg of Ziprasidone Hydrochloride	300	300	300	300	300	300	300	300	300
2.	Crosspovidone	22.5	15.75	9	22.5	15.75	9	22.5	15.75	9
3.	SSG	9	9	9	15.75	15.75	15.75	22.5	22.5	22.5
4.	Magnessium stearate	9	9	9	9	9	9	9	9	9
5.	Talc	9	9	9	9	9	9	9	9	9
6.	MCC	100.5	107.25	114	93.75	100.5	107.25	87	93.75	100.5
7.	Total (mg)	450	450	450	450	450	450	450	450	450

Table 2: Evaluation of powder blend containing Inclusion complex and Excipients

Formulation batches	Physical properties				
	Loose bulk density	Tapped bulk density	Hausner's Ratio	Compressibility Index (%)	Angle of repose
F1	0.477	0.508	1.064	6.10	24.22
F2	0.500	0.548	1.09	7.407	25.17
F3	0.481	0.515	1.07	6.60	24.90
F4	0.469	0.499	1.06	6.012	26.02
F5	0.474	0.506	1.06	6.32	25.57
F6	0.485	0.520	1.072	6.73	24.82
F7	0.472	0.523	1.10	9.75	26.89
F8	0.483	0.518	1.072	6.75	25.76
F9	0.491	0.533	1.085	7.87	25.01

Table 3: Evaluation of Ziprasidone Hydrochloride Fast Dissolving Tablets

Formulation batches	Parameters			
	Thickness (mm) ±SD(n=3)	Hardness (Kg/cm^2) (± SD) (n=3)	%Drug content (± SD) (n=3)	Friability(%) (± SD) (n=30)
F1	4.52 ± 0.005	4.83 ±0.288	99.85 ± 0.64	2.154 ± 0.057
F2	4.54 ±0.015	4.93 ± 0.280	98.08 ± 0.39	2.106 ± 0.046
F3	4.55 ±0.017	5.00 ± 0.500	99.95 ± 0.61	2.136 ± 0.063
F4	4.54 ±0.015	4.89 ± 0.289	98.18 ± 1.20	2.130 ± 0.031
F5	4.53 ±0.021	4.98 ± 0.577	98.82 ± 0.82	2.149 ± 0.031
F6	4.52 ±0.010	5.05 ± 0.577	99.36 ± 0.64	2.088 ± 0.034
F7	4.55 ±0.011	5.10 ± 0.281	99.99 ± 1.51	2.160 ± 0.050
F8	4.54 ±0.020	4.99 ± 0.29	98.62 ± 0.75	2.153 ± 0.021
F9	4.53 ±0.017	4.95± 0.866	99.26 ± 0.29	2.100 ± 0.040

Formulation Batches	Parameters		
	Weight variation (± SD)(n=20)	Wetting time (sec.)(± SD)	Disintegration Time (sec.)(± SD)
F1	442.2±0.134	50.33± 2.08	49.33±2.08
F2	445.0±1.25	54.67±1.53	42.67± 2.08
F3	447.1±0.10	51.0 ±2.00	48.67±2.52
F4	448.06±1.12	49.0 ±2.65	50.0±2.00
F5	447.88±0.49	51.33± 1.53	52.67 ±1.53
F6	448.91±0.02	47.0±1.73	46.33±2.51
F7	449.12±0.93	53.0±2.64	54.33± 1.53
F8	447.67±0.04	57.67± 1.53	40.67± 2.08
F9	448.95±1.38	45.33 ±2.08	45.67± 2.30

Table 4: Dissolution Data of Fast Dissolving Tablets of Ziprasidone Hydrochloride

Formulation	Time (min)									
	2	4	6	8	10	12	14	16	18	20
F1	16.11 ±0.13	28.35 ±0.81	38.40 ±1.31	44.56 ±0.81	51.82 ±1.13	63.54 ±0.76	70.54 ±0.67	79.03 ±0.73	87.20 ±0.50	96.13±0.13
F2	13.89 ±0.51	24.73 ±0.47	32.53 ±0.42	39.73 ±1.19	48.77 ±1.2	50.12 ±0.85	59.66 ±0.33	74.39 ±0.13	85.86 ±0.58	93.15 ±0.83
F3	16.19 ±0.66	26.52 ±1.16	43.26 ±1.01	49.43 ±1.24	64.84 ±0.55	68.80 ±0.58	71.41 ±0.83	81.41 ±0.73	84.81 ±0.73	94.85 ±0.55
F4	15.39 ±0.38	26.54 ±0.33	34.70 ±1.02	40.83 ±0.75	46.24 ±0.55	55.35 ±0.40	63.76 ±0.50	72.20 ±0.48	87 ±0.40	92.3 ±0.13
F5	13.95 ±1.11	25.74 ±0.42	35.87 ±0.35	40.84 ±0.40	47.36 ±1.15	53.83 ±0.61	63.04 ±0.48	68.15 ±0.13	78.06 ±0.58	89.70 ±0.81
F6	12.42 ±0.81	23.55 ±0.61	31.00 ±0.63	38.91 ±0.86	44.34 ±0.58	50.44 ±0.13	58.09 ±0.13	70.2 ±0.87	77.87 ±0.86	92.07 ±0.61
F7	19.14 ±0.28	32.79 ±1.39	41.08 ±0.66	47.21 ±0.87	52.64 ±0.50	64.36 ±0.34	73.19 ±0.40	86.50 ±0.86	94.72 ±0.61	98.25 ±0.87
F8	14.31 ±0.68	27.25 ±0.53	35.88 ±0.73	43.81 ±0.53	51.08 ±0.67	66.48 ±0.65	67.56 ±0.46	77.11 ±0.40	82.75 ±0.07	92.38 ±0.53
F9	12.06 ±0.86	29.07 ±1.34	39.94 ±0.47	43.49 ±0.90	48.46 ±0.40	60.2 ±1.14	66.82 ±0.07	77.81 ±0.46	84.53 ±0.65	93.36 ±0.90

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