International Journal of PharmTech Research
CODEN (USA): IJPRIF ISSN : 0974-4304
Vol.6, No.3, pp 959-968, July-Aug 2014

Design and Evaluation of Sustained Release Tablets containing Solid dispersion of Ziprasidone hydrochloride

M. Madhavi Latha, V. D. Sundar*, S. Nandha Kumar, M. D. Dhana Raju

Research Labs, GIET School of Pharmacy, NH–16 Chaitanya Knowledge City, Rajahmundry-533296, AP, India.

***Corres.author: sundarvd@yahoo.co.in**
Mobile – 091 9959212600

Abstract: In the present investigation an attempt has been made to enhance the solubility and dissolution rate, thereby increasing bioavailability and improved patient compliance by developing sustained release matrix tablets of ziprasidone hydrochloride. Ziprasidone hydrochloride solid dispersions were prepared with PEG 6000 and β-cyclodextrin. The efficient dispersions was further directly compressed to sustained release tablets with matrix polymers like guar gum and HPMC K15 in the ratios of 1:0.5, 1:1, 1:1.5. Precompression and post compression parameters were carried out along with compatibility studies and in vitro drug release studies. The influence of polymers on the release rate and mechanism of drug release for ziprasidone hydrochloride from matrix tablets were determined. The mechanism of release of drug from the formulations was observed to be diffusion controlled exhibited by higher correlation with Higuchi kinetics. To confirm the exact mechanism of drug release from these tablets, the data were fitted to korsemeyer-peppas equation. Slope values >0.5 suggested that the release of Ziprasidone Hcl from the sustained release solid dispersion tablets revealing the fickian drug transport mechanism.
Key words: Ziprasidone HCL, β-Cyclodextrins, guar gum, PEG 6000, HPMC K15, solid dispersion, matrix tablets.

Introduction

In recent years due to application of combinational chemistry and high-throughput screening during drug discovery, a majority of new drug candidates exhibits poor aqueous solubility. A suitable pharmaceutical approach is usually practiced in industries to improve the dissolution of poorly water soluble drugs. The approach indulged in optimizing the formulation parameters, manufacturing process and physicochemical properties of drug for enhancement of dissolution rate.

A poorly water soluble drug will require more time to dissolve in the gastrointestinal fluid than it takes to be absorbed in the gastrointestinal tract[1]. A greater understanding of dissolution and absorption behaviors of drugs with low aqueous solubility is required to successfully formulate them into bioavailable drug products. Although salt formation, particle size reduction etc, have commonly been used to increase dissolution rate of the drug, there are practical limitations with these techniques that the desired bioavailability enhancement may not always be achieved. Therefore formulation approaches are being explored to enhance bioavailability of poorly water-soluble drugs, one being solid dispersion technique[2] and should be formulated as suitable dosage form.

Conventional dosage forms such as capsules, tablets can be considered to release their active ingredients into an absorption pool immediately. The concept of sustained release formulations was designed to achieve a

prolonged therapeutic effect by continuously releasing medication over an extended period of time after administration of a single dose and to eliminate the need for multiple dosage regimens, particularly for those drugs requiring reasonably constant blood levels over a long period of time[3]. In addition, it also has been adopted for those drugs that need to be administered in high doses where too rapid release is likely to cause undesirable side effects. Numerous hydrophilic polymers have been investigated and are currently used in design of sustained release systems[4,5,6] . Polymers like HPMC K15, guar gum[7] are mainly used in the design of sustained release drug in which achieving optimal drug concentration at the site of action is the major challenge.

Ziprasidone hydrochloride is an atypical antipsychotic agent approved by FDA for the treatment of schizophrenia, mania and mixed states associated with bipolar disorder[8]. It is white to off white crystalline powder. It is relatively insoluble in water (21.12 mg/l)[9] and soluble in methanol and DMSO. Its oral bioavailability is 60% and has 99% plasma protein binding. It is hepatically metabolized by aldehyde reductase; minor metabolism occurs via cytochrome P450 3A4 (CYP3A4)[8,10]. Elimination half life of Ziprasidone HCl is 4-5 h. Potential advantages of this drug include low incidence of sedative effects, a low likelihood of extrapyramidal symptoms. For acute psychotic symptoms in patients with schizophrenia, schizoaffective disorder or acute mania, Ziprasidone Hcl is administered twice daily dose of 80 – 160 mg, where as 40 mg/day may be an effective maintenance dose. Based on the above physicochemical and biopharmaceutical properties, Ziprasidone Hcl was selected as a drug candidate[8]. Attempts was made to enhance the solubility of the drug by exploiting the solid dispersion technique and achieve an extended drug release with reduced frequency of drug administration, reduced side effects and improved patient compliance.

Experimental

Materials

Ziprasidone HCL was obtained from Cadila Health Care, Mumbai, India. HPMC K15 was obtained from Himedia, Mumbai, India. PEG 6000, Guar gum, MCC, Methanol were obtained from Merck, Mumbai, India. Magnesium stearate and β-cyclodextrin were obtained from SDFCL, Mumbai, India.

Methods

Preparation of solid dispersions for Ziprasidone Hcl

Solid dispersions prepared by physical mixing

Physical mixtures were prepared by mixing the accurately weighed (1:1, 1:2 and 1:4) Ziprasidone Hcl with PEG 6000 and β-cyclodextrin by spatulation for 10 min.

Solid dispersions prepared by common solvent evaporation method

Solid dispersions were prepared using different ratios (1:1, 1:2, 1:4) of Ziprasidone Hcl and PEG 6000.The required amounts of drug and polymer were weighed and mixed with sufficient amount of methanol. The solvent was allowed to evaporate at room temperature and subsequently dried in an oven at 60^{o}C. The dried residue is pulverized using a glass mortar and pestle. The pulverized mass is sieved #60 to obtain uniform particle size and stored in a desicator at room temperature.

Solid dispersions prepared by kneading method

Solid dispersions were prepared by using different ratios (1:1, 1:2, 1:4) of Ziprasidone Hcl and β-cyclodextrin. The required amounts of drug and polymer were weighed and mixed in a mortar & kneaded with small volume of water-methanol mixture for half an hour to produce homogenous dispersion. The slurry obtained is dried in an oven at 60^{o}C until dryness. The dried residue is pulverized using a glass mortar and pestle. The pulverized mass is sieved #60 to obtain uniform particle size and stored in a desicator at room temperature.

The composition of various formulations of physical mixtures (PM) and solid dispersions (SD) was shown in the table 1.

Table 1: Composition of physical mixtures and solid dispersions

Fomulation code	Designation	Drug:PEG 6000:β-cd
F1	PM	1:1:0
F2	PM	1:2:0
F3	PM	1:4:0
F4	PM	1:0:1
F5	PM	1:0:2
F6	PM	1:0:4
F7	SD	1:1:0
F8	SD	1:2:0
F9	SD	1:4:0
F10	SD	1:0:1
F11	SD	1:0:2
F12	SD	1:0:4
1 part equivalent to 200mg		

Evaluation of physical mixtures and solid dispersions

Evaluation of physical mixtures and solid dispersions were carried out by estimating drug content, DSC, FTIR and *invitro* dissolution studies. Drug content of Ziprasidone HCL was analysed by measuring the absorbance of standard and samples at 317 nm using the UV/Vis spectrophotometer. The FTIR spectroscopy and DSC thermograms were studied to ensure that no chemical interaction between the drug and polymer had occurred.

The *invitro* drug release study of formulations F1-F12 were performed using USP type II dissolution testing apparatus in phosphate buffer. Accurately weighed amount of pure drug, physical mixture and solid dispersion equivalent to 100mg of pure drug was placed in dissolution apparatus with 900ml of deaerated dissolution medium which was run at 75rpm at constant temperature $37^{o}C\pm 1^{o}C$. Samples (5ml) were withdrawn at 0, 5, 10, 15, 20, 30, 45 and 60min, filtered through 0.45 µm whatmann filter, diluted suitably and analysed spectrophotometrically at 317 nm. The best formulation suitable for preparing sustained release tablets was selected on the basis of *in vitro* release studies of physical mixtures and solid dispersions of Ziprasidone HCl prepared with PEG 6000 and β-cyclodextrin.

Preparation of matrix tablets

The sustained release tablets consisting of Ziprasidone HCL solid dispersion and MCC along with matrix polymers like guar gum and HPMC K15 were prepared by direct compression process. The polymer concentration was varied while the drug content (40mg) and the total weight of the tablet (350mg) were kept constant. The ingredients were individually passed through #60 sieve and mixed for 15 min. The mixture was lubricated with magnesium stearate and compressed into tablets using a tablet punching mini press. The composition of various tablet formulations was shown in the table 2.

Table 2: Composition of various sustained release tablet formulations

Ingredients (mg/tablet)	**T1**	**T2**	**T3**	**T4**	**T5**	**T6**
Solid Dispersion (β-CD, 1:4)	200	200	200	200	200	200
HPMC K15	20	40	60	-	-	-
Guar Gum	-	-	-	20	40	60
Microcrystalline cellulose	123	103	60	123	103	60
Magnesium stearate	7.0	7.0	7.0	7.0	7.0	7.0
Total weight	**350**	**350**	**350**	**350**	**350**	**350**

Evaluation of tablets

The prepared matrix tablets were tested as per standard procedures for weight variation (n=20), hardness (n=6), drug content (n=6) and friability (n=20)[11]. Matrix tablet hardness was determined by using a Monsanto tablet hardness tester (SESCO). Friability test was conducted using the Roche friabilator (SESCO). Drug content of ziprasidone HCl was analyzed by measuring the absorbance of standard and samples at 317 nm using the UV/Vis spectrophotometer (PERKIN ELMER).

FTIR spectral analysis

The FTIR analysis was carried out to identify the compatibility between the drug and excipients. A Perkin-Elmer spectrum (Lambda 25) equipped with LITA detector was used for infrared analysis. Samples were prepared by KBr disc method and examined in the transmission method. A resolution of 4 cm^{-1} was used over a frequency range of 4000-450 cm^{-1}.

Differential scanning colorimetry (DSC)

The physicochemical compatibilities of the optimized formulations were tested by differential scanning calorimetric (DSC) analysis. Thermal characterization of pure drug and formulation were performed with mettler Toledo, USA. About 10 mg of sample was placed in sealed aluminum pan. The equipment was calibrated with indium. The samples were scanned at 200 C/min from 50-4000C.

***In vitro* dissolution studies**

Drug release from the prepared tablets was assessed by dissolution test under the following conditions: USP type II dissolution apparatus (ELECTRO LAB PVP08L, MUMBAI, INDIA) at 75 rpm using 900 ml of 0.01 N HCL (2 hr) and phosphate buffer solution, P^H 7.4 (12 hr) as dissolution media. Dissolution studies were carried out for tablet formulations equivalent to 40mg of pure drug maintaining the sink conditions. Total 5 ml aliquot of samples were withdrawn at regular time intervals, filtered and assayed spectrophotometrically at 317 nm. The amount of drug release was determined using an appropriate standard curve. The dissolution profiles of formulations were presented as percent drug release vs. time curves.

Drug release kinetics

To analyse the mechanism of drug release from the matrix tablets, the *in vitro* dissolution data for the best formulations were analysed according to zero-order model, first-order model, Higuchi model and korsemeyer model respectively[12].

Results and Discussion

All formulations were produced under similar conditions to avoid processing variables. Drug content of formulations (F1-F12) was assayed spectrophotometrically at 317 nm. The drug content in these formulations varied between 95.7 % and 102.2 % (average 98.95).

Evaluation of physical mixtures and solid dispersions

The FTIR spectra of solid admixtures of pure drug and various polymers had shown more or less similar peak with almost the same normalized energy, indicating that the drug is unaffected in the presence of various excipients used in the preparation of solid dispersions. The IR spectrum of pure Ziprasidone HCl showed strong broad peak at 3412 cm^{-1} may be due to N-H stretching, 2928.7cm^{-1} may be due to C-H bending, 1629.5cm^{-1} may be due to C=N, 1381.85 cm^{-1} may be due to –C-N, 743.70 cm^{-1} may be due to C-Cl. The FTIR results were given in table 3 and spectra in figure 1- 3.

Table 3: Results of FTIR studies for Physical Mixtures and Solid Dispersions

Sample	Wavelength of the peak				
	N-H	C-H	C=N	C-N	C-Cl
API	3412	2928.7	1629.5	1381.85	743.70
API + PEG	3416.5	2890.9	1632.46	-	841.89
API + β-CD	3367	2920.6	1715.55	1382.87	743.96

Figure 1: F T IR spectrum of Ziprasidone HCl

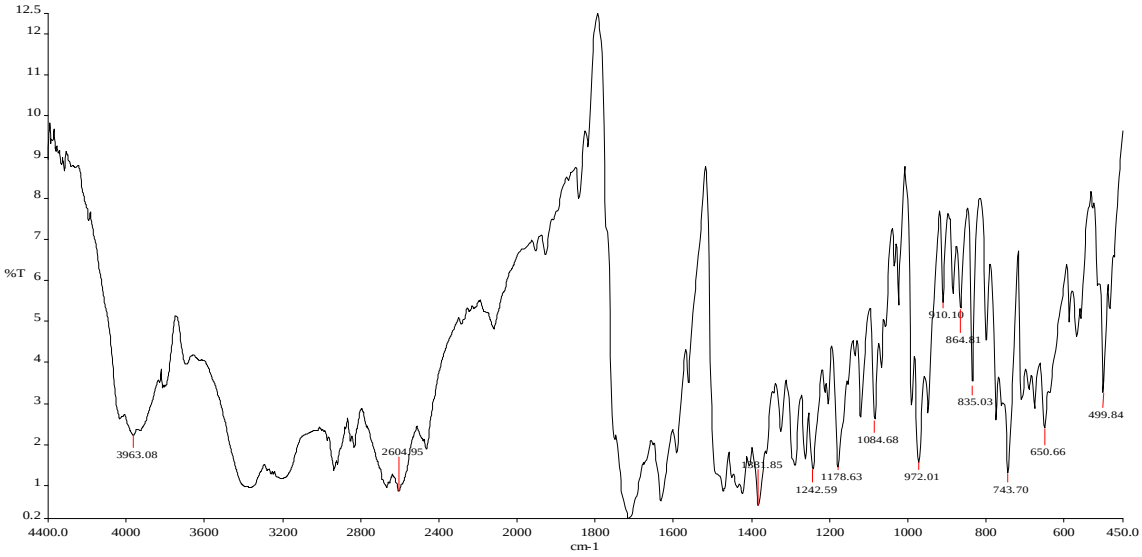


Figure 2: F T IR spectrum of Ziprasidone HCL and PEG 6000

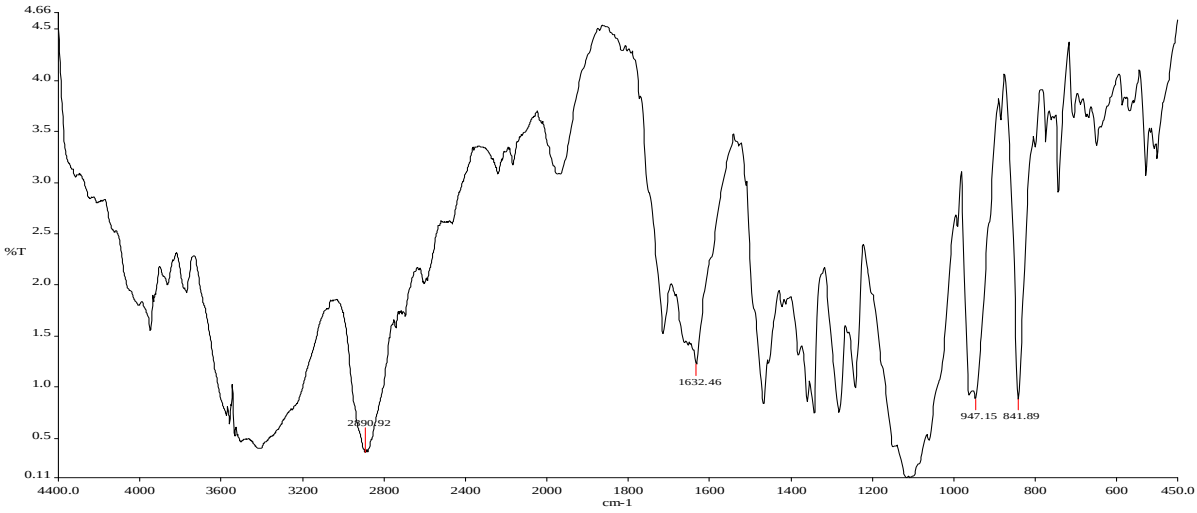
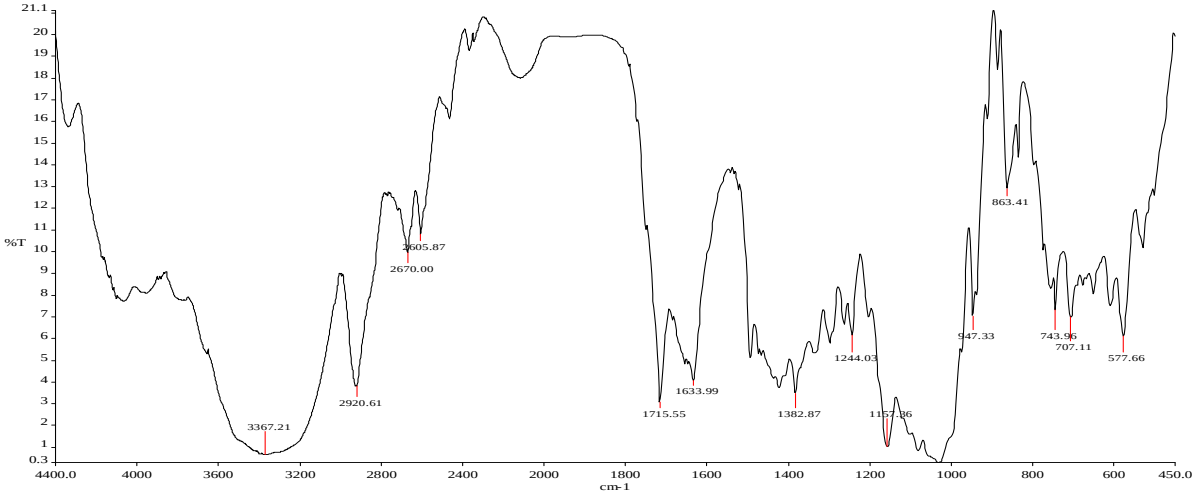


Figure 3: F T IR spectrum of Ziprasidone HCL and β-cyclodextrin



DSC analysis was performed for the pure drug and for formulations F6 and F12 which shows an onset of peak at 262.28°C, 250.11°C and 256.83°C respectively. Ziprasidone hydrochloride exhibits a sharp peak at 262.28°C presented in fig 4. The absence of endothermic peak at 262.28°C for formulations F6 and F12 (fig 5-6) indicated that the drug is uniformly distributed and there is no sign of interaction between drug and polymer. This indicated that there was no drug and polymer interaction.

The *in vitro* drug release study of formulations F1-F12 were performed using USP type II dissolution testing apparatus in phosphate buffer. The results were shown in figure 7 and 8. The dissolution rate was significantly increased with increase in polymer ratio. The mean percentage release of drug from physical mixtures prepared with PEG 6000 and β – cyclodextrin at the ratio of 1:1, 1:2 and 1:4 after 60 mins was found to be 39.9%, 49.7%, 60.07% and 58.3%, 63%, 80.9% respectively. The mean percentage release of drug from solid dispersions prepared with PEG 6000 and β – cyclodextrin at the ratio of 1:1,1:2 and 1:4 after 60 mins was found to be 42.9%, 52.7%, 65.1% and 68.6%, 79.1%, 94.70% respectively.

The solid dispersions prepared by kneading method (F12) containing one part of drug and four parts of β-cyclodextrin exhibits a maximum release of 94.70% within an hour, which was concluded that among all the batches F12 was found to best formulation which is suitable for compression of solid dispersions into an sustained release matrix tablets.

Figure 4: DSC thermogram of Ziprasidone HCl

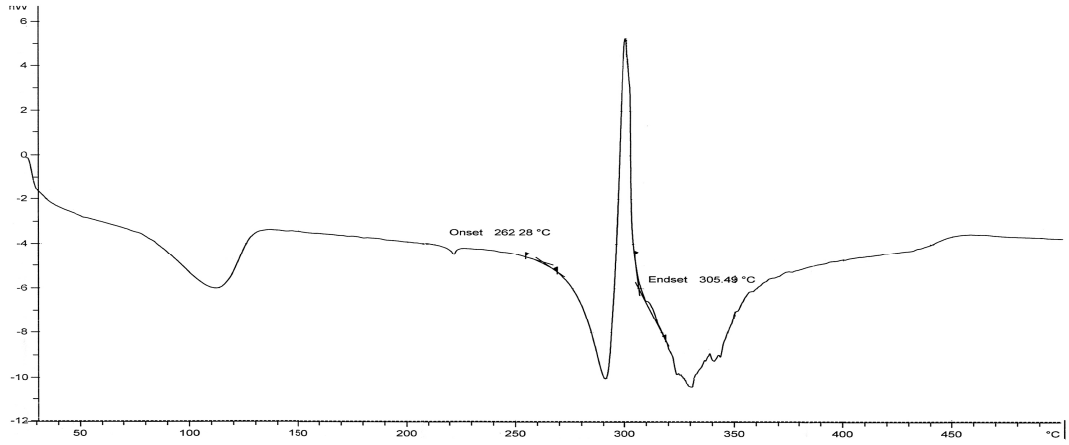


Figure 5: DSC thermogram of β-CD 1:4 physical mixture

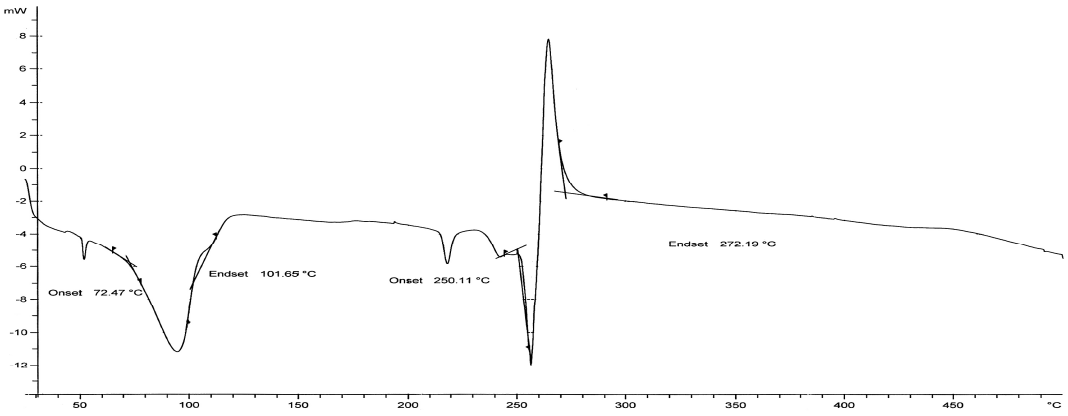


Figure 6: DSC thermogram of β-CD 1:4 solid dispersion

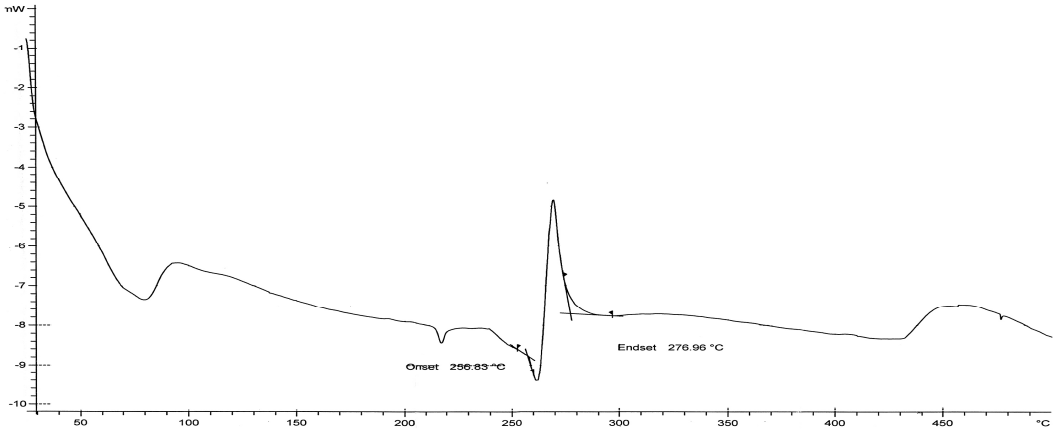


Figure 7: Invitro release profile of formulations F1-F6

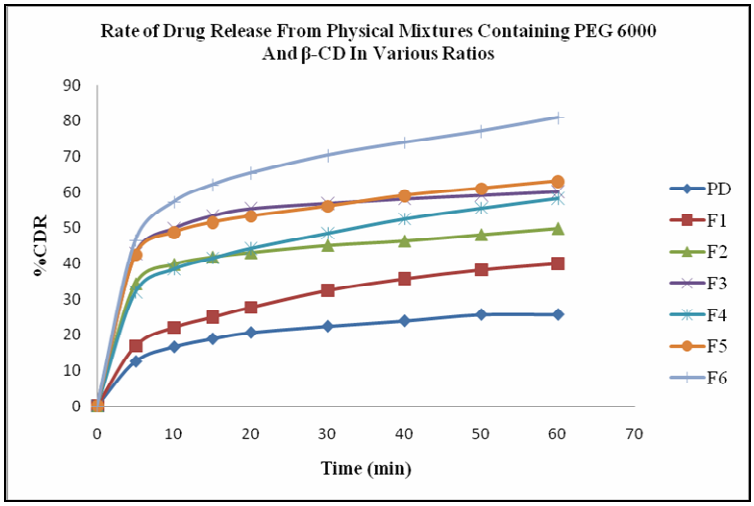
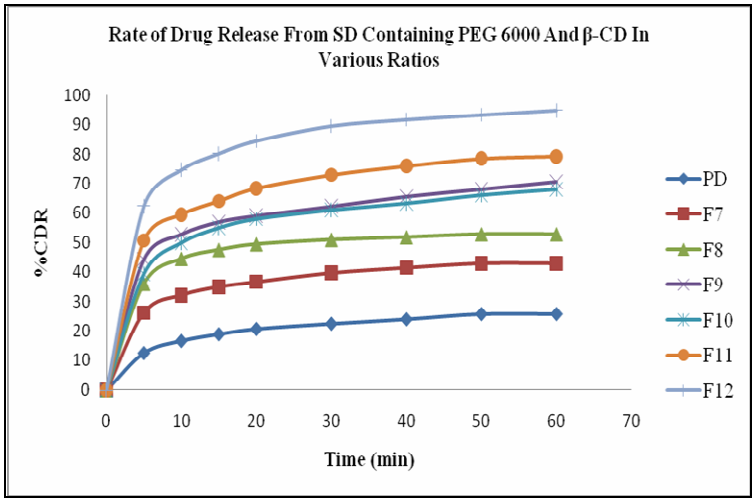


Figure 8: Invitro release profile of formulations F7-F12



Evaluation of tablets

The six tablet formulations T1-T6 containing Ziprasidone Hydrochloride equivalent to 40mg were tested for their mechanical properties i.e. weight variation, hardness, friability and drug content. The results were an average of six tablets from each batch. The variation in weight was within the range of ±5% complying

with pharmacopoeial specifications. The hardness of tablets was found to be 4.5 kg/cm^2. Friability below 1% was an indication of good mechanical resistance of tablets. The drug content in all the formulations was found to be satisfactory indicating content uniformity in the prepared batches. Table 4 proved that all batches were found to be within the limit.

Table 4: Physical properties of tablet formulations

Formulation	Weight uniformity(mg)	Hardness (kg/cm^2)	Friability (%)	Drug content (%)
T 1	349±2.0	4.5±0.3	0.12	98.2±0.5
T2	345±3.0	4.5±0.3	0.20	96.4±0.5
T3	346±3.0	4.5±0.3	0.21	99.9±0.2
T4	351±5.0	4.5±0.3	0.15	100.2±0.3
T5	348±3.0	4.5±0.3	0.18	94.8±0.5
T6	352±3.0	4.5±0.3	0.20	100.6±0.5

Tablet characterization

The FTIR spectra of Ziprasidone Hydrochloride SD (β-CD 1:4) with HPMC K15, Guar gum and microcrystalline cellulose showed a peak at same temperature. No change in shape of spectra observed, indicating that the drug in presence of excipients remains stable. The results were shown in table 5 and spectra in figure 9 -10.

DSC analysis was performed for the pure drug and for optimised matrix tablet formulation, T6 which shows an onset of peak at 262.28^{o}C and 243.93^{o}C respectively. This indicated that there was no drug and polymer interaction. The thermograms were shown in figure 11.

The *in vitro* drug release study of tablet formulations T1–T6 were performed using USP type II dissolution testing apparatus in 7.4 p^H phosphate buffer. The results were shown in figure 12. Among the six batches formulated, the formulation F6 containing guar gum in the ratio of 1:1.5 was found to be best of all the formulations. The release of drug from these batch exhibits a sustained release than the formulations prepared with HPMC K15 as rate retarding polymer. The release rate decreases with increase in polymer concentration.[13]

Figure 9: F T IR spectrum of Ziprasidone HCL, β-cyclodextrin and HPMC K15

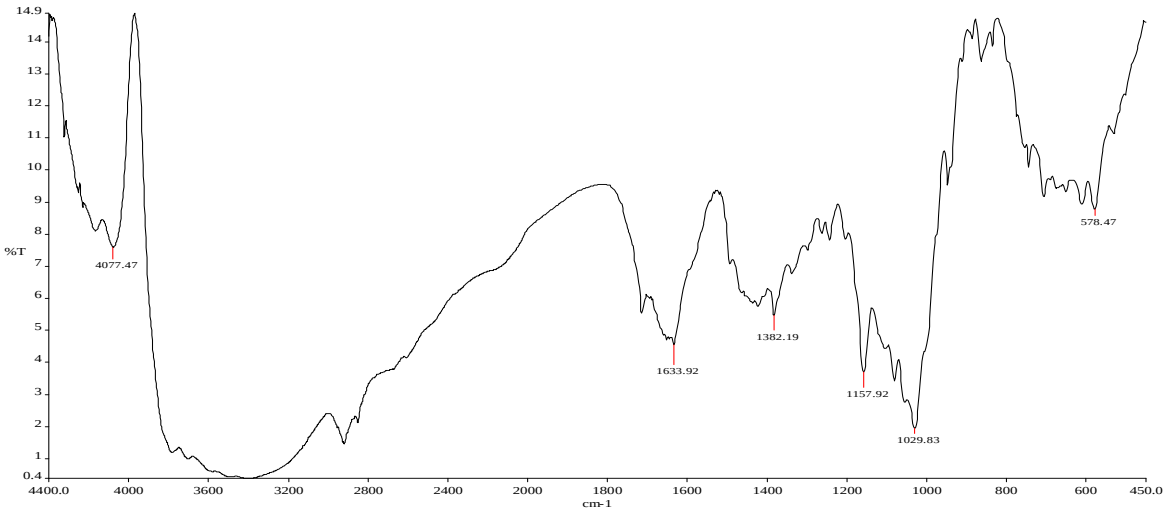


Figure 10: F T IR spectrum of Ziprasidone HCL, β-cyclodextrin and guar gum

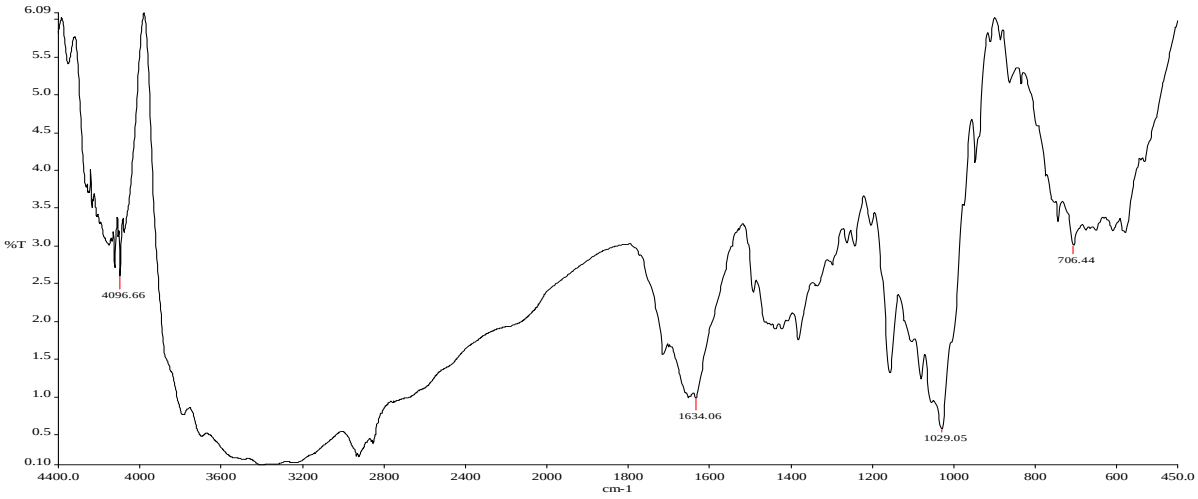


Table 5: Results of FTIR studies for SR Tablets

Sample	Wavelength of the peak				
	N-H	C-H	C=N	C-N	C=Cl
API	3412	2928.7	1629.5	1381.85	1743.70
API+HPMC K15	-	-	1633.92	1382.19	578.47
API + Guar gum	-	2953.5	1634.06	-	706.44

Figure 11: DSC thermogram of tablet with guar gum 1:1.5

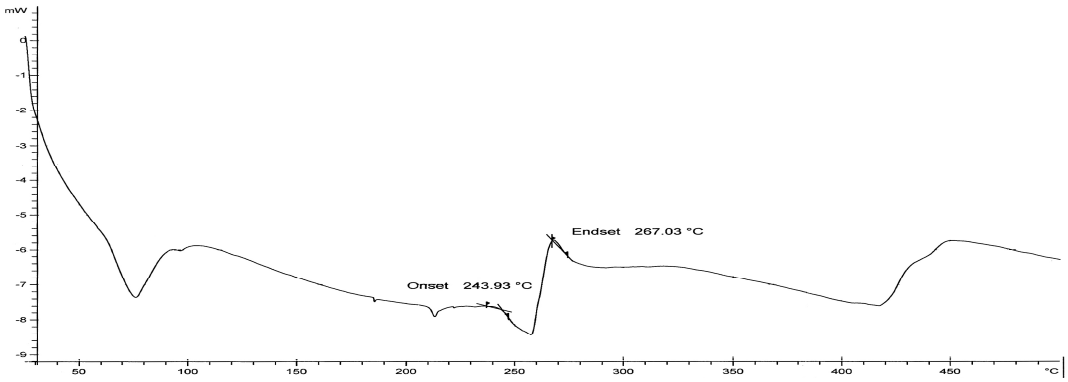
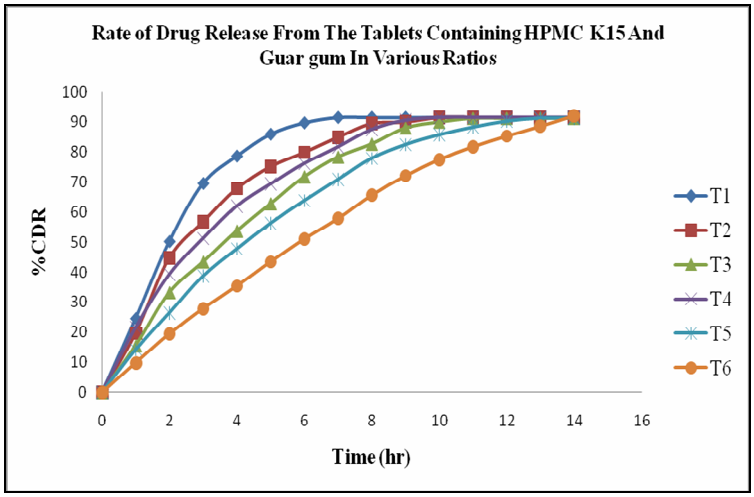


Figure 12: Dissolution profiles of SR tablets containing HPMC K15 and Guar gum



Drug release kinetics:

The in vitro dissolution data for tablet formulations were fitted in different kinetic models i.e, zero order, first order and Higuchi and korsemeyer-peppas equation.The results were summarized in the table 6. Drug release from the tablet follows Higuchi and was confirmed by its fairly linear plots, indicated by their high correlation coefficient 0.9939.

To confirm the exact mechanism of drug release from these tablets, the data was fitted to korsemeyer-peppas equation. The best formulation (T6) shows R^2 value 0.9874 which was highest correlation factor with peppa's kinetics. Slope values >0.5 suggested that mechanism of drug release follows Fickian diffusion.

Table 6: In Vitro Drug Release kinetics

Formulation	Zero Order r^2	First Order r^2	Higuchi r^2	Korsemeyer-peppas	
				r^2	n
T1	0.435	0.6782	0.7009	0.8692	0.156
T2	0.497	0.9279	0.8861	0.9813	0.231
T3	0.531	0.9658	0.9679	0.998	0.368
T4	0.624	0.8399	0.8769	0.9631	0.259
T5	0.678	0.953	0.9516	0.9665	0.315
T6	0.782	0.9841	0.9939	0.9874	0.482

Conclusion

The present study proves that it is possible to increase the solubility and dissolution rate of poorly soluble drug Ziprasidone hydrochloride by preparing it as solid dispersion with β-cyclodextrins by kneading method which was due to solubilizing effect. These solid dispersions exhibited faster dissolution characteristics as compared to that of pure drug. The sustained matrix tablet containing guar gum in the ratio of 1:1.5 was found to be best of all formulations showing sustained release of drug within a narrow range over prolonged period of time. The release of drug from all the formulation followed diffusion controlled release followed by Higuchi which was confirmed by higher correlation coefficient values.

References

1. Horter D, Dressman JB, Influence of physicochemical properties on dissolution of drug in the gastrointestinal tract, Adv Drug Del, 53, 1997, 3-14.
2. James Swarbrick, James C Boylan. Encylopedia of Pharmaceutical Technology, Marcel Dekker: New York, 3, 1992; 337 – 345.
3. Loen shargel, Andrew BC Yu. Applied Biopharmaceutics And Pharmacokinetics 2nd ed. ACC, 1985.
4. Hayashida T, et al. US 5 Patent No. US 1997 593 694.
5. Conte U L, et al. US 5 1997 626 874.
6. Chowhan ZT, Role of binders in moisture induced hardness increase in compressed tablets and its effect on invitro disintegration and dissolution, Journal of Pharmaceutical Sciences, 69(4), 198-202.
7. Sourabh Jain, Yadav SK, UK Patil, Preparation and evaluation of sustained release matrix tablet of Furosemide using natural polymers, Research J. Pharm. And Tech, 1(4), 2008, 374-376.
8. Martindale, The Extra Pharmacopoeia 31st ed. Pharmaceutical press, London 2002.
9. Deshmukh SS, Potnis VV and Kute AB, Development of dissolution medium for Ziprasidone hydrochloride, Indian Pharmacist, 47, 2006, 79-80.
10. Goodman and Gilman. The Pharmacological Basis Of Therapeutics 1oth ed. McGraw-Hill, 2001.
11. United States Pharmacopoeia 25. Rockville, MD, United States Pharmacopoeial Convention Inc, 2007; 1475.
12. Hogan J E, Hydroxypropylmethylcellulose sustained release technology, Drug Dev. Ind. Pharm, 15, 1998, 975-999.
13. Sundramoorthy K, Kavimani S, Vetrichelvam T, Manna PK, Venkappayya D, Formulation and evaluation of extended release dosage form of metformin hydrochloride using combined hydrophobic and hydrophilic matrix tablets, Ind J Pharm edu Res 42, 2008, 232 – 242.

*****