



FORMULATION OPTIMIZATION AND EVALUATION OF ORODISPERSIBLE TABLETS OF ZIPRASIDONE

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ABSTRACT

Ziprasidone Hydrochloride, a Class II drug is an atypical antipsychotic agent, which is poorly water soluble with only 60% bioavailability. In present study attempt has been made to prepare Ziprasidone Hydrochloride fast disintegrating dissolving tablets. For enhancing solubility of drug, inclusion complexes of drug were prepared using BCD and Kyron T-314. These complexes were characterized by solubility study, differential scanning calorimetry and X-ray diffractometry. To aid in faster disintegration of tablets, superdisintegrant in different proportions were used and their effect on disintegration was studied. The inclusion complexes with HPBCD prepared by microwave method exhibited highest enhancement in solubility (0.024g/100ml) and also showed fastest dissolution profile (100% drug release in 5 min.). So this complex was worked further for formulation of Ziprasidone Hydrochloride fast disintegrating/ dissolving tablets. Among the tablet formulations prepared using different superdisintegrants, those with 5 % w/w Polyplasdone showed the lowest disintegration time (21 sec.) and fastest dissolution profile.

Key Words:- Ziprasidone Hydrochloride, BCD, Kyron T-314, Directly Compressible Manitol, Polyethylene Glycol.

INTRODUCTION

The major problem faced by many patients with conventional tablet dosage form is difficulty in swallowing. This problem is more apparent when drinking water is not easily available to the patient taking medicine. Hence patients may not comply with prescription, which results in high incidence of ineffective therapy (Seager H, 1998). The fast dissolving drug delivery system is rapidly gaining acceptance as an important novel drug delivery system. This delivery system offers better patient compliance than conventional tablet dosage form (Indurwade NH *et al.*, 2002). Bioavailability of drug from this delivery system is significantly greater than from conventional tablet (Kuchekar BS *et al.*, 2003).

Ziprasidone Hydrochloride is a newer atypical antipsychotic drug used in treatment of schizophrenia, which is an ongoing mental disease (Chue P *et al.*, 2002). Frequent relapses occur in about 55 % of schizophrenic patients (Chue P *et al.*, 2004), mostly because of medication noncompliance as it depends upon route of administration and type of dosage form used. Thus there is an obvious need for development of fast disintegrating /dissolving tablets to overcome patient noncompliance. Ziprasidone Hydrochloride is practically insoluble in water (BCS Class II) (Loftsson T *et al.*, 2004). Like other drug candidates in this class, this drug also has solubility-limited bioavailability (60%). Hence prior to its formulation as mouth disintegrating tablets it was decided to improve its solubility by complexation with BCD (Suresh S *et al.*, 2006).

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EXPERIMENTAL

Materials

Ziprasidone Hydrochloride was obtained as a gift sample from Wockhardt Pharmaceutical. BCD, Kyron T-314, Directly Compressible Mannitol, Microcrystalline Cellulose, Talc, Polyethylene Glycol, (S.D.Fine Chemicals Ltd, Bombay) were used. All other chemicals and reagents used were of analytical grade.

Methods

a) Phase solubility analysis for Ziprasidone Hydrochloride

Phase solubility studies were performed to determine stoichiometric proportions of Ziprasidone Hydrochloride with BCD and Kyron T-314. Also this data was used to determine the stability constant of complexes. For this, the stock solutions of 0.01 M of BCD and Kyron-314 were prepared separately using distilled water. These stock solutions were appropriately diluted with distilled water to give molar solutions in the range of 0.002 to 0.01 for both BCD and Kyron T-314. Five ml of each molar solution was filled in screw-capped vials and the excess quantity of drug was added to each vial separately. The vials were kept for shaking at ambient temperature for 48 hrs using a lab shaker (Remi). The supernatant solutions were collected carefully and filtered using Whatman filter paper (No.41). The absorbances of resultant solutions were recorded at 317nm (Loftsson T, Brewster ME, 1996).

b) Preparation of inclusion complexes by microwave irradiation method

The required molar (1:1) quantities of drug and Cyclodextrin were weighed accurately and transferred to round bottom flask. Minimum amount of solvent mixture (Methanol: Water=1:1 v/v) was added to this. The mixture was reacted for two minutes at 600C in the microwave oven. After reaction was complete, adequate amount of solvent mixture was added to remove the residual free drug and BCD or Kyron T-314. Precipitate so obtained was separated using Whatman filter paper (No.41). It was dried in vacuum oven at 400C for 48 hrs. Faint pink colored powder was obtained which was then stored in airtight containers till further use (Wen X *et al.*, 2004).

c) Characterization of Ziprasidone Hydrochloride inclusion complexes

Inclusion complexes of Ziprasidone Hydrochloride were characterized by following analytical techniques.

i) Estimation of drug content

The quantities of inclusion complex equivalent to

10mg of Ziprasidone Hydrochloride were dissolved in Water/Methanol mixture (1:1). Appropriate dilutions were made and drug content of each complex was calculated.

ii) Saturation solubility studies

Solubility study was performed according to method reported by Higuchi and Connors (Higuchi T, Connors KA, 1965). Excess quantities of inclusion complexes were added to 25 ml distilled water taken in stoppered conical flasks and mixtures were shaken for 24 hrs in rotary flask shaker. After sufficient shaking to achieve equilibrium, 2ml aliquots were withdrawn at 1 hr intervals and filtered through Whatman filter paper no. 41. The filtrate so obtained was analyzed spectrophotometrically at 317 nm. Shaking was continued until three consecutive readings were same.

iii) IR spectral analysis

Infra red spectra of drug and its inclusion complexes were recorded by KBr method using Fourier Transform Infrared Spectrophotometer (FTIR-8400s). A base line correction was made using dried potassium bromide and then spectra of dried mixtures of drug and inclusion complexes with potassium bromide were recorded (Arias MJ *et al.*, 2000).

iv) X – ray diffraction (XRD) study

The X ray diffraction pattern of the selected inclusion complexes was compared with that of the pure Ziprasidone Hydrochloride. This was done by measuring 2θ in the range of 4 to 500 with reproducibility of ± 0.0010 on a diffractometer (Philips). The XRD patterns were recorded automatically using rate meter with time constant of 2×10^2 pulse/second and with the scanning speed of 20 (2θ)/min (Arias MJ *et al.*, 2000).

v) Differential scanning calorimetric (DSC) analysis

This study was performed using DSC model (Perkin Elmer). For this study, the samples were placed in a platinum crucible and the thermograms were recorded at a heating rate of 100C/min in the range of 200C to 310⁰C (Arias MJ *et al.*, 2000).

vi) Dissolution studies of Ziprasidone Hydrochloride and its inclusion complexes

The quantity of inclusion complex equivalent to 20 mg of Ziprasidone Hydrochloride was placed in dissolution medium and apparatus was run maintaining following test conditions. [Dissolution medium- 900 ml of phosphate buffer pH 7.4 containing 1% w/v sodium lauryl sulphate, Speed of paddle- 75 rpm, Temperature of dissolution medium- 370C \pm 0.50C, Apparatus type - USP

XXII (paddle)]. Aliquots of 10 ml were withdrawn at time intervals of 5, 10, 15, 20, 25, 30, 40, 50 and 60 min. The volume of dissolution medium was adjusted to 900 ml by replacing each 10 ml aliquot withdrawn with 10 ml of fresh dissolution medium. The concentrations of drug in samples were determined by measuring absorbances at 317 nm. Cumulative percent drug released was determined at each time point. Pure drug was used as control.

d) Development of rapidly disintegrating tablets by direct compression method

Fast disintegrating tablets were prepared using BCD inclusion complexes of Ziprasidone hydrochloride. The formula included variable amounts of superdisintegrants and other excipients. The resulting powder blends were evaluated for flow parameters. The powder blends equivalent to the 20 mg of drug were directly compressed into tablets using 8.45 mm flat faced round punches. The superdisintegrants used were Directly Compressible Mannitol, Lactose and Magnesium Stearate in concentration range of 25 mg, 86 mg for ZCP1 and ZKT1, 83.5 mg for ZCP2 and ZKT2 and 81 mg for ZCP3 and ZKT3 and magnesium Stearate 2 mg individually. Table I gives compositions of these tablet formulations. F9 was a control formulation containing no superdisintegrants. Final weight of each tablet was kept constant (250mg) by varying the weight of microcrystalline cellulose i.e. Avicel (PH 102). Tablets were evaluated for various parameters (Bi YX *et al.*, 1999).

Evaluation of tablet characteristics

The tablets were evaluated for weight variation, uniformity of drug content, *in vitro* disintegration time and *in vitro* dissolution behavior.

Dissolution study

The tablets from the formulation (F1-F9) were subjected to dissolution test using USP Dissolution Test Apparatus Type II maintaining following parameters [Dissolution medium- 900 ml of phosphate buffer pH 7.4 containing 1% w/v sodium lauryl sulphate, Apparatus type - USP XXII (paddle), Speed 75 rpm, Temperature of dissolution medium- $37.0\text{C} \pm 0.50\text{C}$.] All the dissolution tests were carried out in triplicate.

RESULTS AND DISCUSSION

Phase solubility analysis of Ziprasidone Hydrochloride

Phase solubility study was performed to determine the stoichiometric proportion of Ziprasidone Hydrochloride with complexing agent BCD and Kyron T-314. The phase solubility analysis indicated formation of a

1:1 molar inclusion complex of drug with BCD and Kyron T-314. Apparent stability constant (KC) was found to be 674 K-1 and 1218 K-1 for BCD and HPBCD complexes respectively.

Preparation of inclusion complexes of Ziprasidone Hydrochloride

Inclusion complexes of Ziprasidone Hydrochloride with BCD and HPBCD prepared by microwave irradiation method found to be slightly pink, free flowing powders.

Characterization of Ziprasidone Hydrochloride inclusion complexes

Inclusion complexes of Ziprasidone Hydrochloride with BCD and HPBCD showed consistency in drug content (almost 100 %). Cyclodextrins and their derivatives are proved to be powerful solubilizers for many poorly water-soluble drugs. In present work also significant enhancement in the solubility of drug was observed for inclusion complexes with cyclodextrins. The saturation solubility of inclusion complexes of Ziprasidone Hydrochloride with BCD and HPBCD were found to be 0.020 ± 0.91 g/100ml and 0.024 ± 0.80 g/100ml respectively which is far superior to solubility of pure drug 0.0024 ± 0.23 g/100ml.

i) IR spectral analysis

IR spectra of inclusion complexes of Ziprasidone Hydrochloride with BCD and HPBCD are given in Fig.1. Analysis of IR spectra of inclusion complexes revealed the disappearance of characteristic peaks of aromatic C-H stretching and N-H stretching at 3250 cm^{-1} and 3400 cm^{-1} respectively. While the peak at 1750 cm^{-1} (carbonyl stretching of lactum ring) remained intact, it therefore, suggests that vibrating and bending movements of guest molecule i.e. Ziprasidone hydrochloride were restricted due to formation of inclusion complexes. It may be the aromatic ring portion of Ziprasidone Hydrochloride which has been included into the cavity of BCD.

ii) X – ray diffraction study of inclusion complexes of Ziprasidone Hydrochloride

Ziprasidone Hydrochloride, HPBCD and inclusion complexes of drug with HPBCD prepared by Microwave method were subjected to XRD analysis (Fig 2). From the figure, it was evident that pure drug existed as microcrystalline particles as many broad peaks of very low intensity were observed. However no sharp peaks were detected. The X-ray diffraction pattern for inclusion complexes was characterized by complete absence of any diffraction peak for the drug, suggesting probable

transformation of microcrystalline form into an amorphous state (Higuchi T, Connors KA, 1965).

iii) Differential scanning calorimetric analysis

Ziprasidone Hydrochloride, HPBCD and inclusion complexes of drug with HPBCD prepared by microwave method were subjected to DSC analysis. The thermograms are given in Fig. 3. The thermogram of pure drug showed broad endothermic peak ranging from 400C to 1300C due to loss of water of hydration. It confirms monohydrate salt form of drug. It also showed small endothermic peak at 3000C corresponding to its melting point. The DSC thermogram of HPBCD was characterized by an endothermic peak at about 2800C. DSC thermogram of inclusion complex of drug with HPBCD showed sharp endothermic peak at around 2600C corresponding to melting of Kyron T-314. Also broad endotherm of drug ranging from 500C to 1400C was observed, it might be due to loss of water molecule from drug. The formation of inclusion complex is suggested by disappearance of endothermic peak at melting point of drug.

iv) Dissolution studies of Ziprasidone Hydrochloride and its complexes

The inclusion complexes of Ziprasidone Hydrochloride with both cyclodextrins produced pronounced enhancement in its dissolution (Fig. 4). HPBCD (100 % drug release within 5 min.) was found to be more effective than BCD (100 % drug release within 25 min.) in enhancing the dissolution rate of drug as compared to pure drug alone (only 55 % drug release within 60 min.)

d) Development of rapidly disintegrating tablet formulation by direct compression method

The present work was undertaken to formulate and evaluate fast disintegrating Ziprasidone Hydrochloride tablets by direct compression method. Superdisintegrants at different concentration levels (3 % w/w, 4 % w/w, 5 % w/w) were included to assist faster disintegration. The absorption of water is an important step for subsequent disintegration process of tablets. Bi et.al.⁽¹²⁾ Have reported that when higher concentrations of superdisintegrant were added to tablet formulations, they absorbed considerable amount of water and resulted in increase in viscosity of fluid within the tablet mass. This delayed further water penetration into the tablets. Therefore, it was decided to use superdisintegrant concentrations only up to 5% w/w. Bi et.al.⁽¹³⁾ also reported that tablets containing excessive large amounts of water-soluble fillers such as Tablet exhibited slower disintegration of tablets. The probable reason cited was that after dissolution of Tablet, the

channels in fiber structure widened considerably allowing its swelling which then offered less help in rapid disintegration of tablets. Hence it was decided to use water insoluble filler like Micro crystalline cellulose to overcome this problem. Mannitol was used for its sweet taste and negative heat of solution, which leaves a pleasant cooling sensation in mouth.

e) Evaluation of tablets

All batches of prepared tablets were evaluated for preliminary evaluation tests like weight variation, hardness and friability, and found within the range as per USP standards. The critical evaluation parameters have been discussed here.

i) Evaluation of effect of concentration of superdisintegrant on disintegration time of tablets

All tablet formulations indicated disintegration time in between 15.33 to 29.67 sec. The control formulation (F10) showed disintegration time of 50.67 sec. From these findings it can be claimed that the addition of the superdisintegrants has certainly improved the disintegration rate of tablets. Among the three superdisintegrants used, HPBCD showed less disintegrating time followed by BCD and Micro crystalline cellulose. The probable reason may be high gelling tendency of HPBCD and Micro crystalline cellulose than BCD which causes swelling of tablet mass with subsequent retardation of disintegration (Bi XY *et al.*, 1999).

Besides the type, the concentration of superdisintegrant used also affected the disintegration time. In case of the tablets containing BCD and Kyron T-314, an increase in concentration of superdisintegrant resulted in definite decrease in disintegration time. The same result was found for tablets containing Micro crystalline cellulose up to 4 %. At 5 % concentration, it resulted in slight increase in disintegration time from 25 sec. to 27 sec. This delay in disintegration time might have occurred due to probable blockade of capillary pores in tablet mass as a result of formation of the viscous plug by Micro Crystalline cellulose particles, which subsequently prevented free access of fluid into tablets. The disintegration time for all tablet formulations was also evaluated "*in vivo*" in healthy volunteers. For all formulations "*in vivo*" disintegration time values were more than corresponding "*in vitro*" values. This may be due to low volume of saliva available and weak agitation in the mouth as compared to *in vitro* test (Koizumi K *et al.*, 1997).

ii) Evaluation of effect of concentration of superdisintegrant on drug release profile from tablets

Dissolution profile of control tablet formulation that is formulation without addition of any superdisintegrant (F10) showed 100% drug release within 8 min. Three different levels of superdisintegrant concentrations; 3 %w/w, 4 %w/w and 5 %w/w were used to assess the effect of their increasing concentrations on release profiles of drug from tablets. The dissolution rate was found to increase linearly with increasing concentrations of Superdisintegrant. This was marked by decreased disintegration time values for tablet formulations containing higher proportions of superdisintegrants except for tablet containing 5 % HPBCD. Formulations F1, F2, F3, which contained increasing concentrations of BCD from 3%w/w to 5%w/w, have recorded 100% drug release within 5 min., 4

min. and 2 min. respectively. Formulations F4, F5, F6, which contained increasing concentrations of Micro crystalline cellulose from 3 %w/w to 5 %w/w, have recorded 100% drug release within 5 min., 4 min. and 3 min. respectively. Formulations F7, F8, F9 contained increasing concentrations of HPBCD i.e. 3 %w/w, 4 %w/w and 5 %w/w respectively. All of them have recorded 100% drug release within 5 min. But T90 values indicated that with the increase in concentration of HPBCD from 3 %w/w to 4 %w/w, the rate of dissolution of tablets was slightly enhanced. However further increase in concentration to 5 %w/w did not improve the dissolution rate but infact retarded it. This was probably due to formation of the viscous plugs by Primojel particles. The relative efficiency of different superdisintegrants to improve the dissolution rate of tablets was in order, Polyplasdone > AC Di Sol > Control.

Figure 1. IR Spectra of complexes of Ziprasidone HCl

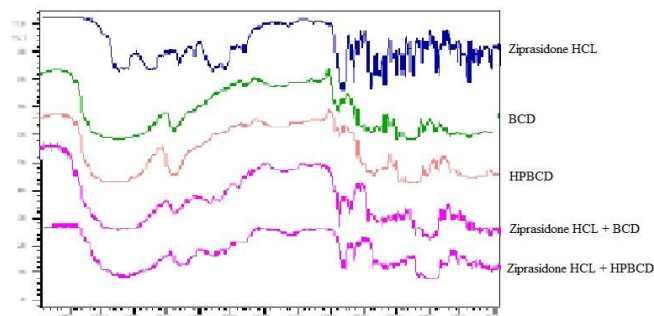


Figure 3. DSC Pattern of Ziprasidone HCl

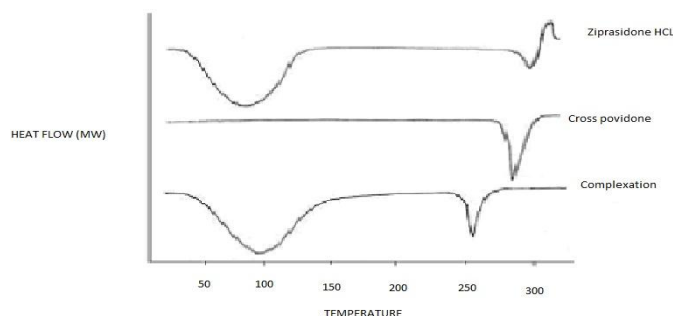


Figure 5. % Cumulative drug release of batch ZKT1 to ZKT3

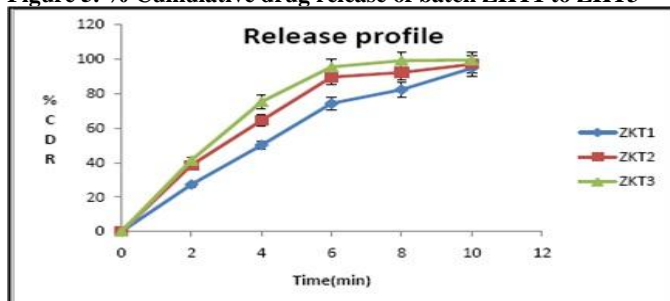


Figure 2. XRD Pattern of Ziprasidone HCL

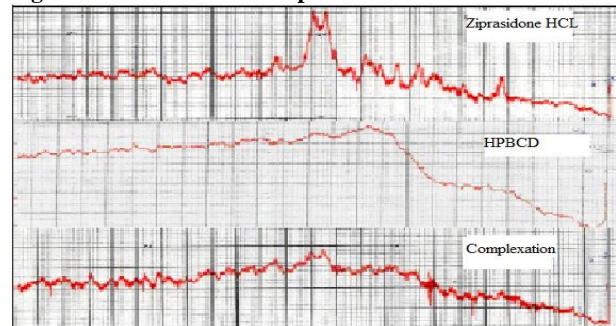


Figure 4. % Cumulative drug release of batch ZCP1 to ZCP3

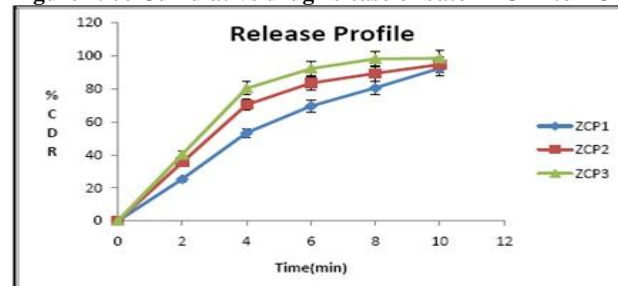


Figure 6. % Cumulative drug release of batch ZF1 to ZF9

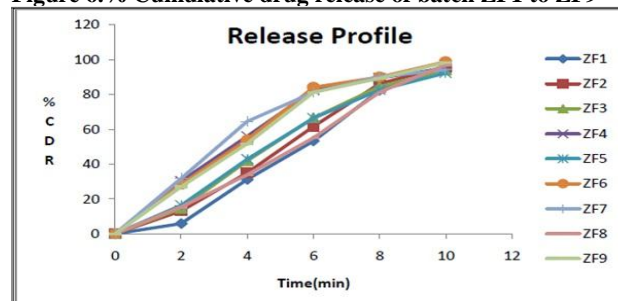


Table 1. Formulation of complex with cyclodextrins

Ingredients(mg)	ZCP1	ZCP2	ZCP3	ZKT1	ZKT2	ZKT3
Amount of solid dispersion equivalent to 20 mg of drug	120	120	120	120	120	120
BCD	2.5	5	7.5	-	-	-
HPBCD	-	-	-	2.5	5	7.5
Mannitol	25	25	25	25	25	25
Lactose	86	83.5	81	86	83.5	81
Magnesium Stearate	2	2	2	2	2	2
Talc	2	2	2	2	2	2
MCC	12.5	12.5	12.5	12.5	12.5	12.5
Total	250	250	250	250	250	250

CONCLUSION

Fast dissolving tablets prepared by the BCD in 4% concentration are promising for rapid release of Ziprasidone HCl. Incorporation of solid dispersion (PEG 4000 : Ziprasidone HCl) (4:1) into BCD in 2 % concentration enhanced the release rate of Ziprasidone HCl and thus therapeutic levels of the drug could be achieved through fast dissolving tablets. Prepared tablets exhibited first order kinetics and the drug release profile was matrix diffusion type. From this study it is possible to design suitable fast dissolving tablets containing

Ziprasidone HCl for the treatment of psychoses with more effectiveness and better patient compliance. Further *in-vivo* investigations are required to correlate *in-vitro* drug release studies for the development of suitable rapid release system for Ziprasidone HCl.

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