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SOLUBILITY ENHANCEMENT OF BCS CLASS II DRUG USING LYOPHILISATION TECHNIQUE AND DETERMINATION OF BIOAVAILABILITY IN ANIMALS USING CATALEPSY MODEL

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Keywords:

Bioavailability, Inclusion complex, Lyophilisation, Ziprasidone HCl

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ABSTRACT: Ziprasidone HCl is a newly introduced atypical antipsychotic drug. It has its own unique multi receptor binding affinity. This makes it a unique special choice of antipsychotic agent. It mainly acts as antagonist of D_2 dopamine receptors as and $5HT_2A$ (serotonin, 5HT, 5-hydroxytryptamine) receptors. It is pinkish brown colored powder having very low solubility in water (21.12 mg/L). The main purpose of this study is to enhance the solubility of Ziprasidone HCl using lyophilisation technique. The β-Cyclodextrine and Hydroxy Propyl- β-Cyclodextrine were used as the water soluble carriers for increasing the solubility of Ziprasidone. All the inclusion complexes prepared by lyophilisation technique showed remarkable increase in the solubility compared to the pure Ziprasidone HCl. The saturation solubility analysis demonstrated highest increase in the solubility of drug after complexation with HP-β-CD by lyophilisation technique. The inclusion complexes were characterized using DSC and XRD technique. During *in vitro* study result obtained that the lyophilized complexes with HPβ-CD showed 100% drug release within 10 min were as the lyophilized complexes with β– CD showed 100% drug release in 25 min. Therefore the freeze dried complex with HP-β-CD was selected for Catalepsy study on Wistar rats. In the catalepsy study the selected inclusion complex showed increase in bioavailability compared to the drug and almost all the data obtained from study was found to be 99.99% significant with the control.

INTRODUCTION: [1-7] The way of treating psychosis was totally changed when atypical antipsychotics were introduced in the therapy of psychosis. Due to the economic and therapeutic efficacy of second generation antipsychotics these are preferred mostly for the treatment than first generation antipsychotics. Ziprasidone Hydrochloride (HCl) is one of the newly introduced atypical antipsychotic. It has its unique multi receptor binding affinity. This makes it a unique special choice of antipsychotic agent. It mainly acts as antagonist of D2 dopamine and $5HT_2A$ (serotonin, 5HT, 5-hydroxytryptamine) receptors. It is a pinkish brown coloured powder having very low solubility in water (21.12 mg/L). The oral absorption of Ziprasidone is limited and it reaches maximum concentration within 6-7 hours. Therefore it shows poor oral bioavailability. The oral bioavailability is only 39-60% with a $t_{1/2}$ of about 6 hours (Approximately). Complexing with cyclodextrin is one of the most promising techniques to enhance the solubility of poor water soluble moiety. They form a water soluble complex with the drug having very low solubility. The complexes were prepared using various techniques physical mixing, kneading, co-precipitation, solvent evaporation,

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spray drying and freeze drying. In present study β-Cyclodextrine and Hydroxy Propyl- β-Cyclodextrine were used as the water soluble carriers for increasing the solubility of Ziprasidone using lyophilisation technique. All inclusion complexes prepared by lyophilisation technique showed remarkable increase in the solubility compared to the pure Ziprasidone HCl. The saturation solubility analysis demonstrated highest increase in the solubility of drug after complexation with HP-β-CD by lyophilisation technique.

The inclusion complexes were characterized using DSC and XRD technique. The dissolution profiles were calculated and compared with different complexes. The influence of carriers and methods on complexation and physicochemical property of drug–CD complex was investigated to select the most efficient and effective system for improving solubility of Ziprasidone HCl.

MATERIALS AND METHODS: Ziprasidone HCl gift sample was provided by Micro labs Mumbai, India. B-cyclodextrin (BCD) and HP β-CD was provided as gift sample by Gangwal Chemicals Mumbai, India. Other chemicals used were of analytical grade.

Phase Solubility Study: [8] Solubility determinations were performed in triplicate according to the method of Higuchi and Connors. The effect of concentrations of the two Cyclodextrins on the equilibration solubility of Ziprasidone HCl in water at room temperature was carried out by adding an excess amount of drug (25 mg) in to a screw-capped glass vial containing 10 ml of water and various amounts of the carrier (2-10% w/v). The samples were placed on a magnetic stirrer and agitated at room temperature for 48 hrs. An aliquot of each solution was withdrawn and filtered through a Whatman filter paper (no. 41). The assay of Ziprasidone HCl was determined spectrophotometrically at 318 nm (Shimadzu U.V 1800). A plot of molar concentrations of each of β-CD and HPβ-CD vs. molar concentrations of drug was plotted. The stability constant was calculated according to equation:

$$K_{(1:1)} = \text{Slope} / S_o (1-\text{Slope})$$

Methods of preparation of Inclusion complexes: [9, 10, 11, 19, 21, 22, 23]

Physical Mixture: [9, 10] The required molar (1:1) ratio quantities of drug and β-CD/Hp β-CD were weighed and mixed separately in mortar with vigorous trituration. The mixtures were then passed through sieve no. 40 and were stored in airtight container until further use.

Lyophilisation / Freeze drying: [11] The earlier prepared 1:1 physical mixture of the drug was wetted with 1:1 water: methanol mixture and this was kneaded to form a homogeneous suspension. This was then frozen for 24 hrs at -21 ^{0}C and subjected to lyophilisation. The final product was then pulverized and sieved between 50 μm and 200 μm sieves.

Characterization of Inclusion complexes:

Saturation Solubility: [12, 24] Solubility study was performed according to method reported by Higuchi and Connors. Excess quantities of inclusion complexes were added to 25 ml distilled water taken in stoppered conical flasks and mixtures were shaken for 24 hrs. After sufficient shaking to achieve equilibrium, 2 ml aliquots were withdrawn at 1 hr intervals and filtered through Whatman filter paper no. 41. The filtrate so obtained was analyzed spectrophotometrically at 318 nm. Shaking was continued until three consecutive readings were same.

Drug Content Determination: [13] Drug content was determined by dissolving solid dispersion equivalent to 10 mg of the ZPR in small quantity of methanol and kept in ultrasonicator for 10 min. The volume was adjusted to 50ml with 1% SLS in phosphate buffer pH 7.4. The solution was filtered through Whatman filter paper no.41, suitably diluted and the absorbance was measured at 318 nm using double beam U.V. spectrophotometer (Shimadzu U.V 1800).

Infra-Red Analysis: [14] IR absorption spectrum of Ziprasidone HCl and the prepared inclusion complexes were recorded by Attenuated total reflectance (ATR) technique using FTIR spectrophotometer (Shimadzu FTIR-8400s) wherein very small amount of the sample was used.

The resultant spectrum of the drug was compared with reference spectrum of Ziprasidone HCl.

X-Ray Diffraction Analysis: [15] The X- ray diffraction pattern of the sample of inclusion complexes was compared with that of the pure Ziprasidone HCl. This was done by measuring 2ø in the range of 4 ° to 50 ° with reproducibility of ±0.0010 on a diffractometer (Philips). The XRD patterns were recorded automatically using rate meter with time constant of 2 × 102 pulse/second and with the scanning speed of 20 (2ø)/min.

Differential Scanning Calorimetric Analysis (DSC): [16] This study was performed using SII Nanotechnology (SEIKO) instrument. For this study, the samples were placed in an alumina crucible and the thermo grams were recorded at a heating rate of 10 ^{0}C/min in the range of 20 ^{0}C to 400 ^{0}C.

***In-vitro* Drug Release:** [17, 20] The quantity of inclusion complex equivalent to 20 mg of Ziprasidone HCl 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 37 0C ± 0.5 0C, 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 mins.

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 318 nm. Cumulative percent drug released was determined at each time point. Pure drug was used as control.

Catalepsy Study: [18] Groups of 18 male Wistar rats with a body weight between 120 and 250 g were used. They were dosed intraperitoneally with the test drug or the standard. Then, they were placed individually into translucent plastic boxes with a wooden dowel mounted horizontally 10 cm from the floor and 4 cm from one end of the box. The floor of the box was covered with approximately 2 cm of bedding material. White noise was presented during the test. The animals were allowed to adapt to the box for 2 min. Then, each animal was grasped gently around the shoulders and under the forepaws and placed carefully on the dowel. The amount of time spent with at least one forepaw on the bar was determined. When the animal removed its paws, the time was recorded and the rat was repositioned on the bar. Three trials were conducted for each animal at 30, 60, 120 and 360 mins.

RESULT AND DISCUSSION:

Phase solubility study: From phase solubility study the stoichiometric ratio of Ziprasidone HCl and carrier's β-CD and HP- β-CD was determined. Phase solubility analysis showed formation of complexes in 1:1 molar ratios with β-CD and HP β-CD. The value of stability constant was found to be 100.10 M^{-1} and 300.18 M^{-1} for β-CD and HP-β-CD complexes. The results of phase solubility analysis of complexes of Ziprasidone HCl with β-CD and Ziprasidone HCl with HP β- CD are shown in **Table 1**, **Fig. 1** and **Table 2, Fig. 2** respectively.

TABLE 1: RESULTS OF PHASE SOLUBILITY ANALYSIS OF COMPLEXES OF ZIPRASIDONE HCL WITH β-CD

Sr. No	Concentration of BCD (mM)	Concentration in mM/ml
1	0.002	$1.67049x10^{-05}$
2	0.004	$1.84526x10^{-05}$
3	0.006	$2.0223x10^{-05}$
4	0.008	$2.20614x10^{-05}$
5	0.01	$2.49666x10^{-05}$

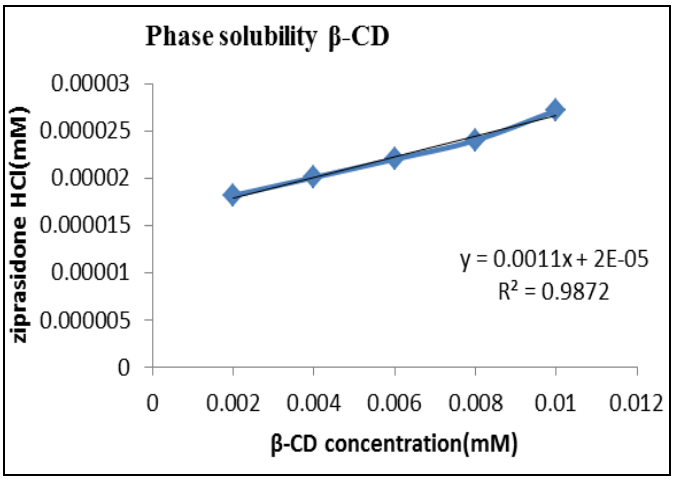

FIG. 1: PHASE DIAGRAM OF COMPLEX OF ZIPRASIDONE HCL WITH β- CD

TABLE 2: RESULTS OF PHASE SOLUBILITY ANALYSIS OF COMPLEXES OF ZIPRASIDONE HCL WITH HP β- CD

Concentration of HPBCD (mM)	Concentration mM/ ml
0.002	$3.383x\ 10^{-06}$
0.004	$4.792x\ 10^{-06}$
0.006	$6.2024x\ 10^{-06}$
0.008	$7.3254x\ 10^{-06}$
0.01	$8.225x\ 10^{-06}$

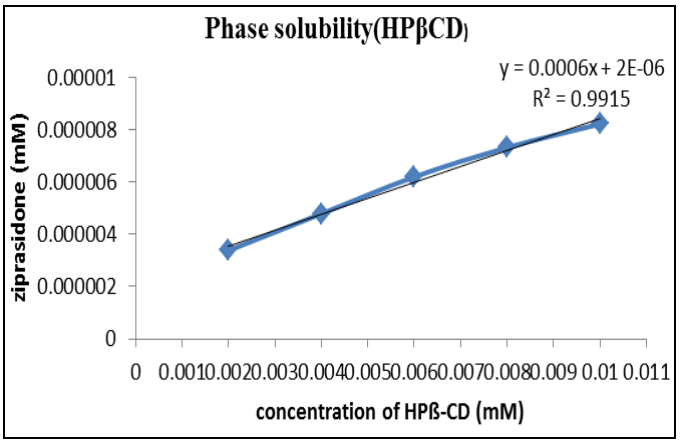

FIG. 2: PHASE DIAGRAM OF COMPLEX OF ZIPRASIDONE HCL WITH HP β- CD

Preparation of Inclusion Complex: Inclusion complexes of Ziprasidone HCl with β-CD and HP-β-CD prepared by different methods were slightly pinkish brown freely flowing powders.

Characterization of Ziprasidone HCl inclusion complexes:

Saturation Solubility: An increase in the saturation solubility of the drug can explain the improved dissolution of solid dispersions, as per the Noyes and Whitney equation, since the saturation solubility of a compound is dependent on the size of the particles (if the particle size is less than 0.1µm). It is possible to achieve such reduction in particle size with solid dispersion systems, hence the saturation solubility studies were performed for these solid dispersion systems using untreated Ziprasidone HCl as a control. The increase in solubility was reported when the drug was formulated into solid dispersion using lyophilisation technique. It was observed that increase in polymer weight fraction in the system had direct effect on enhancement of drug solubility. The solubility of Ziprasidone HCl has definitely increased in presence of cyclodextrins. This increase in the solubility can be attributed to one or more molecular interactions between Ziprasidone HCl and cyclodextrins to form distinct species or complexes. The solubilizing efficiency of the two cyclodextrins was in the order,

$$HP-\beta-CD \ > \ \beta-CD$$

The freeze dried inclusion complex with βCD and HP-βCD showed 556.04 & 783.68 values respectively, for saturation solubility these values were greater than the values of physical mixture. The saturation solubility for HP-βCD and βCD inclusion complexes are shown in **Table 3** and **Fig. 3** and **Table 4** and **Fig. 4** respectively.

TABLE 3: SATURATION SOLUBILITY FOR HP-βCD INCLUSION COMPLEXES

Sr. No.	Complex System	Method of preparation	Ratio of drug carrier	Saturation solubility µg/ml
1.	Pure Drug	-	1:1	19.33±0.11
2.	Ziprasidone HCl: HPβCD	Physical Mixture	1:1	260.97±01.34
6.	Ziprasidone HCl: HPβCD	Freeze drying	1:1	783.68±0.70

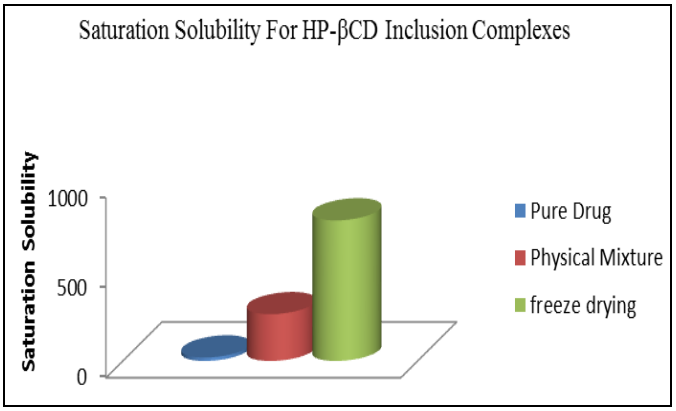

FIG. 3: SATURATION SOLUBILITY FOR HP-βCD INCLUSION COMPLEXES

TABLE 4: SATURATION SOLUBILITY FOR β CD INCLUSION COMPLEXES

Complex system	Method of Preparation	Ratio of Drug Carrier	Saturation Solubility µg/ml ± S.D.
Pure drug	-	-	19.33±0.115
Ziprasidone HCl: βCD	Physical Mixture	1:1	168.74±1.50
Ziprasidone HCl: βCD	Freeze Drying	1:1	556.04±.12

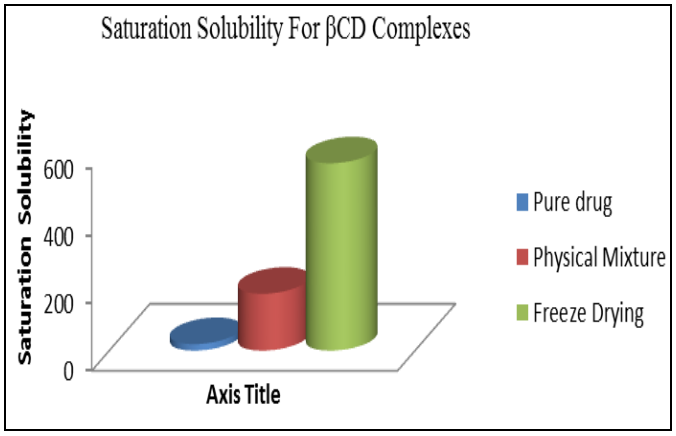

FIG. 4: SATURATION SOLUBILITY FOR INCLUSION COMPLEXES

Drug Content: Inclusion complexes of Ziprasidone HCl with β-CD and HPβ-CD showed good consistency in drug content. The inclusion complexes prepared with HPβ-CD and β-CD showed drug content of almost 99.04 ± 0.93% and 95.31% respectively. Drug content are shown in **Table 5** and **Fig. 5.** The freeze Dried inclusion complexes prepared with HP-β-CD showed the highest amount of drug content as shown in **Table 6** and **Fig. 6.**

TABLE 5: DRUG CONTENT FOR β-CD COMPLEXES

Sr. No.	Techniques	Drug Content
1	Physical mixture	99.80±1.17
2	lyophilized	95.31±0.07

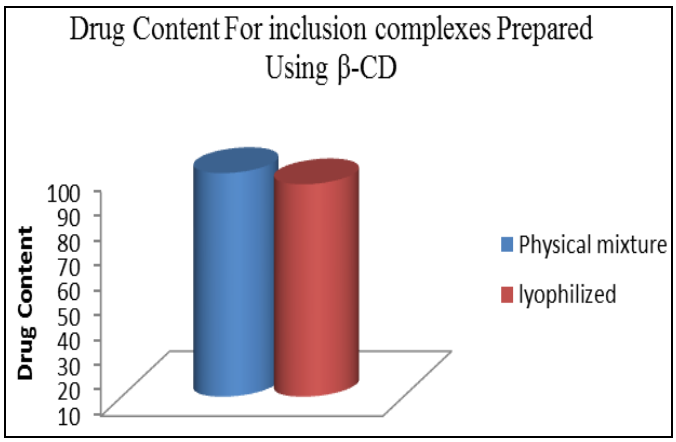

FIG. 5: DRUG CONTENT FOR INCLUSION COMPLEXES PREPARED USING β-CD

TABLE 6: DRUG CONTENT FOR HPβ-CD COMPLEXES

Sr. No	Techniques	Drug Content ± S.D
1	Physical mixture	100.01±1.39
2	Lyophilized	99.04±0.93

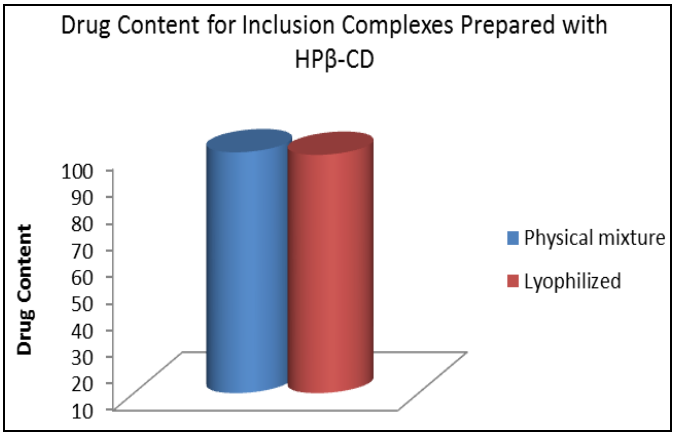

FIG. 6: DRUG CONTENT FOR HP β-CD COMPLEXES

Infra-Red Analysis: The peaks in the range of 3472 cm^{-1} to 3371 cm^{-1} in all these systems are smoothened, which would be due to some host-guest interaction between Ziprasidone HCl and cyclodextrins. The spectra of all physical mixtures indicated intact peaks for pure Ziprasidone HCl as well as pure β – Cyclodextrin (**Fig. 7** and **8**). In all cases however, there was reduction in intensity of Ziprasidone HCl peak which was obscured by cyclodextrin peaks indicating formation of complexes.

Analysis of IR spectra of inclusion complexes prepared by lyophilisation and physical mixtures of components revealed the disappearance of the characteristic peaks of aromatic N– H stretching. This indicates that vibrating and bending of guest molecule was restricted due to formation of inclusion complexes, so very likely aromatic ring of Ziprasidone HCl was inserted into cavity of Cyclodextrins.

IR Data For β-CD Inclusion Complexes:

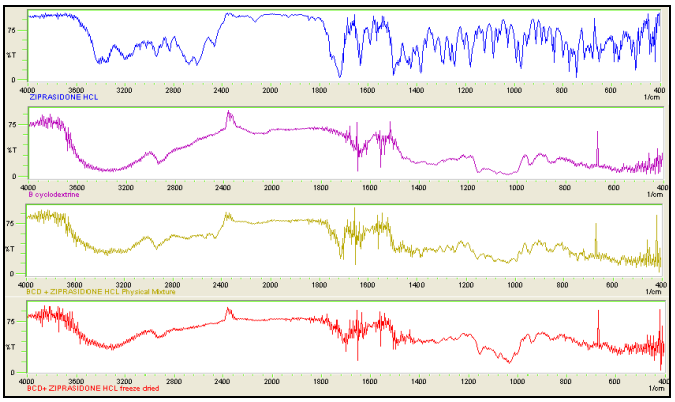

FIG. 7: IR DATA FOR β-CD INCLUSION COMPLEXES

Infra-Red Study for HP β-CD Inclusion Complexes:

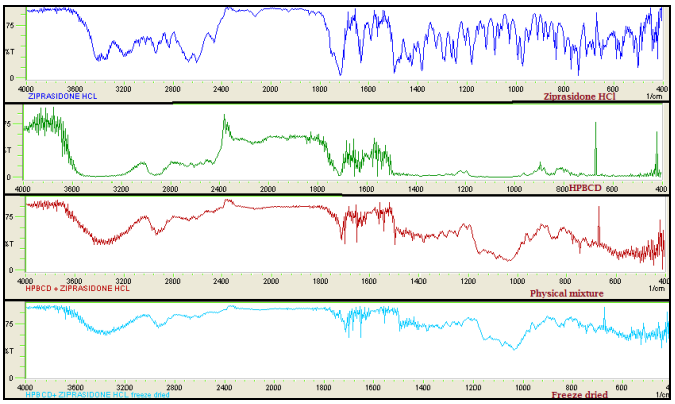

FIG. 8: INFRA-RED STUDY FOR HP β CD INCLUSION COMPLEXES

X-Ray Diffraction Analysis of the Inclusion Complexes: The diffractograms of almost all of the solid dispersions of Ziprasidone HCl and cyclodextrin prepared by various methods, showed decrease in diffraction peaks for both Ziprasidone HCl pure and cyclodextrin pure thus indicating conversion from crystalline state to amorphous state (**Fig. 9** and **10**). These findings suggests that the observed enhancement in dissolution rate of drug was due to the reduction of crystalline nature which was achieved by the formation of complex between pure drug and cyclodextrins.

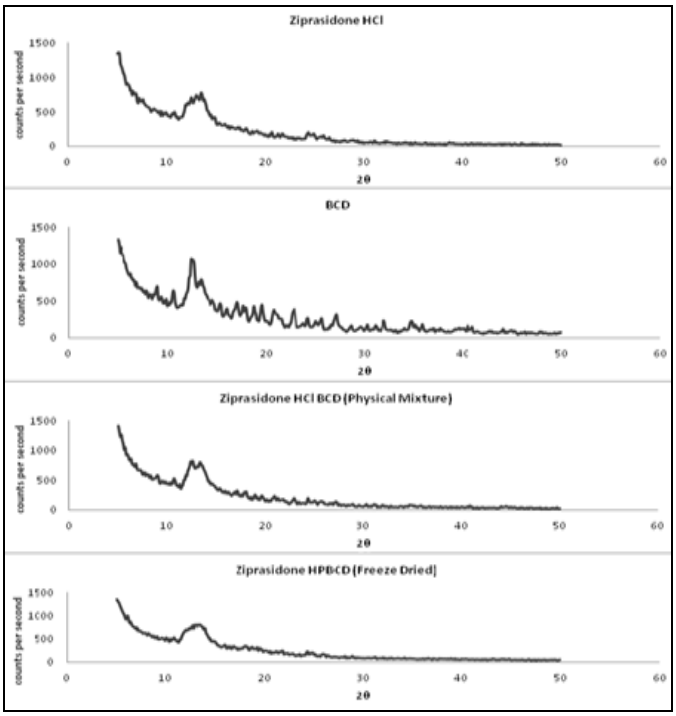

FIG. 9: X-RAY DIFFRACTION STUDY FOR β CD COMPLEXES

X-Ray Diffraction Study for HP β-CD Inclusion Complexes:

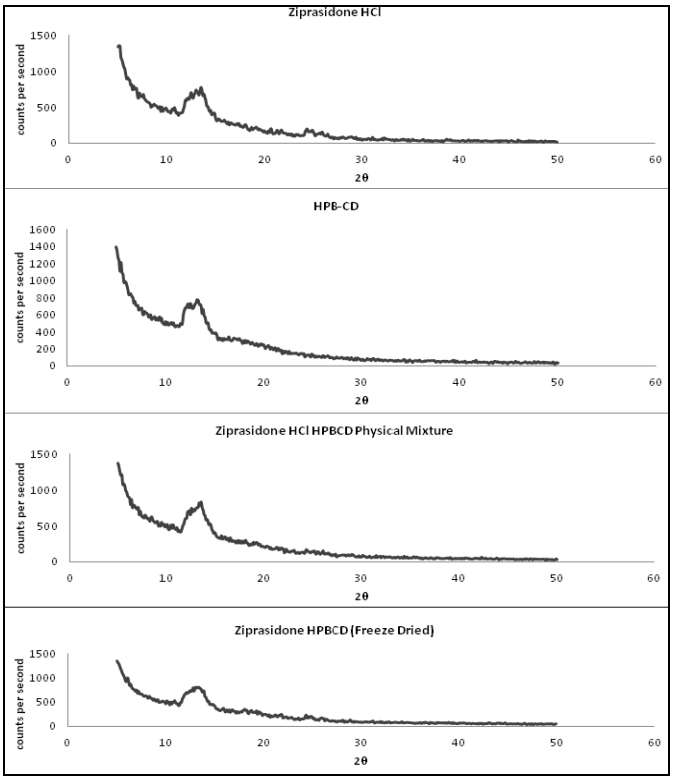

FIG. 10: X-RAY DIFFRACTION STUDY FOR HP-β-CD INCLUSION COMPLEXES

DSC Analysis of Inclusion Complexes: The DSC thermogram of Ziprasidone HCl showed a sharp melting endotherm at 307 ^{0}C corresponding to its melting point (**Fig. 11**). The DSC thermogram of β – CD was characterized by an endothermic peak at about 238.3 ^{0}C (**Fig. 12**). In case of Ziprasidone HCl: β– CD, 1:1 M complex (prepared by lyophilisation technique Fig. 14), there was marked reduction in the intensity and/or broadening of the Ziprasidone HCl at around 259.8 °C indicating partial inclusion of Ziprasidone HCl in the cyclodextrin cavity.

DSC Thermograms for Ziprasidone β-CD Complexes:

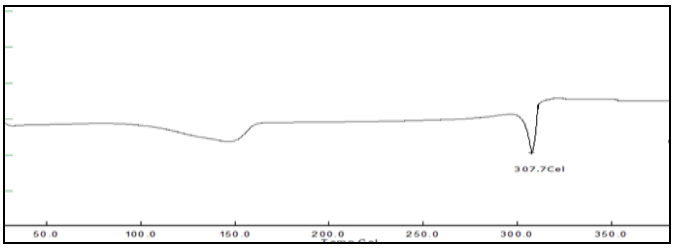

FIG. 11: DSC PATTERN FOR ZIPRASIDONE HCL (PURE)

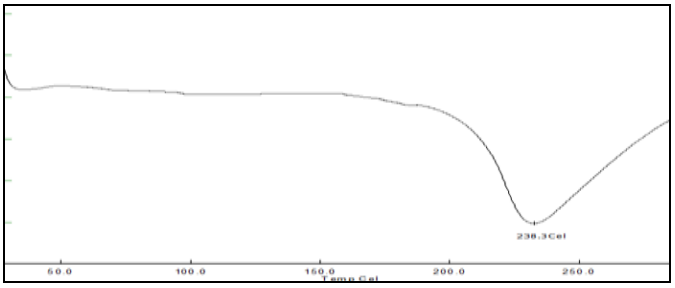

FIG. 12: DSC PATTERN FOR β-CD (PURE)

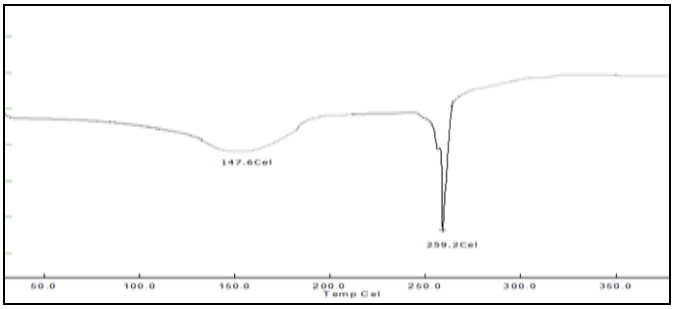

FIG. 13: DSC PATTERN FOR PHYSICAL MIXTURE

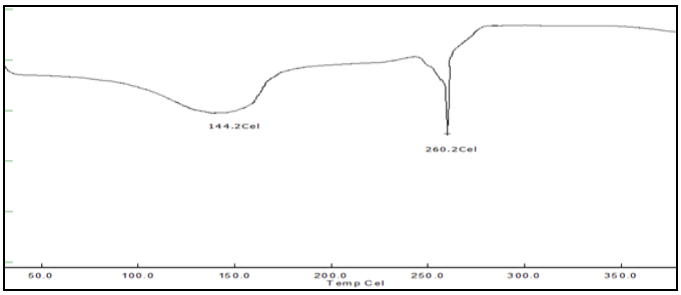

FIG. 14: DSC PATTERN FREEZE DRYING

DSC Thermograms for HP-β- CD Inclusion Complexes:

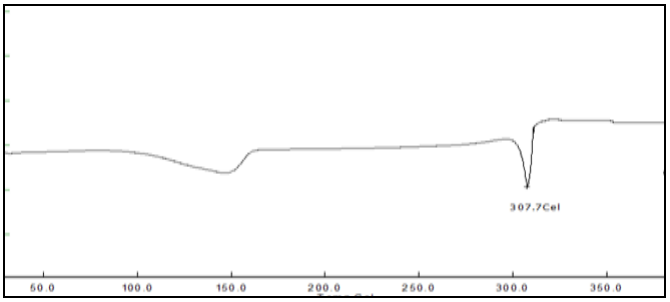

FIG. 15: DSC PATTERN FOR ZIPRASIDONE HCL (PURE)

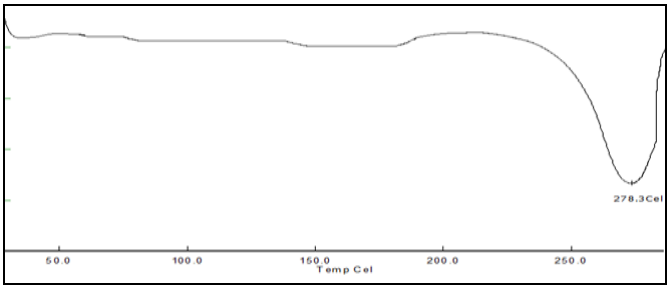

FIG. 16: DSC PATTERN FOR HP-β-CD (PURE)

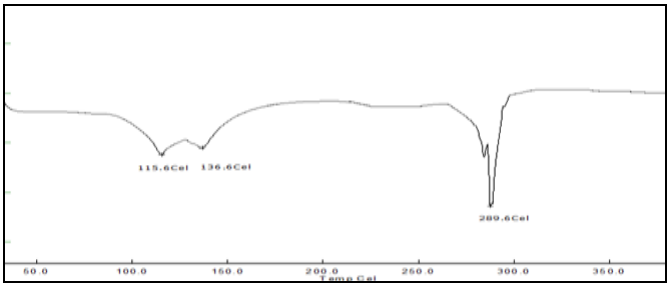

FIG. 17: DSC PATTERN FOR PHYSICALLY MIXED ZPN HP β-CD COMPLEX

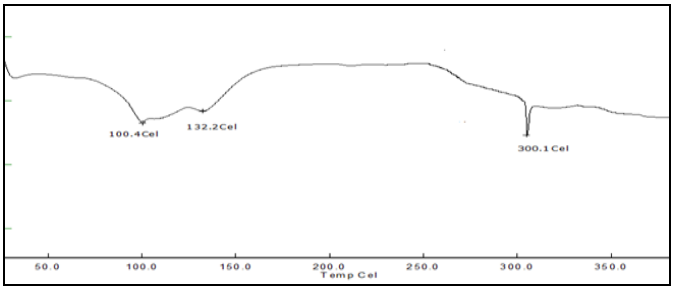

FIG. 18: DSC PATTERN FOR LYOPHILIZED ZPN HP β-CD COMPLEX

***In-vitro* Analysis of Inclusion Complexes:** Two different polymers *i.e.* BCD and HP β-CD were used in ratio 1:1 to assess the effect of two different polymers on the drug release profile of Inclusion Complexes. In both the cases, resulted in definite improvement in the rate and the extent of drug dissolution *i.e*. dissolution rate of dispersions were increased. The probable reasons for this may include a facilitation of dissolution of Ziprasidone HCl, by the dissolved carrier and also a decrease in its particle size in the solid dispersion. The lyophilized complexes with HPβ-CD showed 100% drug release within 10 mins were as the lyophilized complexes with β– CD showed 100% drug release in 25 mins. From *in-vitro* dissolution study and saturation study it was decided to select Complexes prepared with HPβ-CD by freeze drying for animal study to detect its bioavailability. Percentage drug release for β-CD and HPβ-CD complexes are shown in **Table 7, Fig. 19** and **Table 8**, **Fig. 20**..

TABLE 7: PERCENTAGE RELEASE FOR INCLUSION COMPLEXES WITH β-CD

Time	Pure Drug	Freeze dried	Physical mixture
0	0	0	0
5	0.50 ±0.012	9.11±0.11	0.091±0.02
10	1.60±0.34	19.79±0.31	0.73±0.06
15	3.21±0.56	35.76±0.45	1.83±0.053
20	5.14±0.31	65.14±0.61	3.94±0.076
25	7.57±0.41	99.98±0.13	7.57±0.042
30	11.99±0.23		12.98±0.055
35	16.79±0.62		18.49±0.035

40	21.94±0.91	24.28±0.77
45	27.59±0.11	31.25±0.67
50	33.82±0.39	39.10±1.67
55	40.39±0.28	47.04±0.51
60	47.59±0.32	56.18±0.54

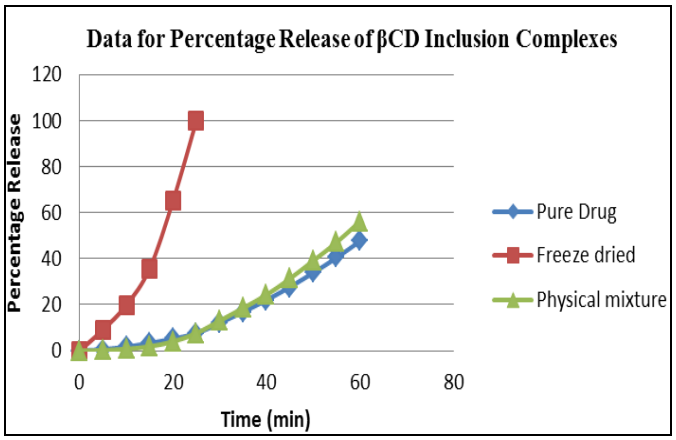

FIG. 19: PERCENT RELEASE FOR β-CD COMPLEXES

TABLE 8: PERCENTAGE DRUG RELEASE FOR HP β-CD COMPLEXES

Time	Pure Drug	Freeze Dried HPBCD	Physical Mixture HPBCD
0	0	0	0
5	0.50	44.54	0.82
10	1.60	100.012	1.69
15	3.20		3.1
20	5.14		5.73
25	7.57		8.58
30	11.97		12.30
35	16.79		18.13
40	21.94		24.14
45	27.58		31.57
50	33.82		40.07
55	40.31		48.61
60	47.59		59.48

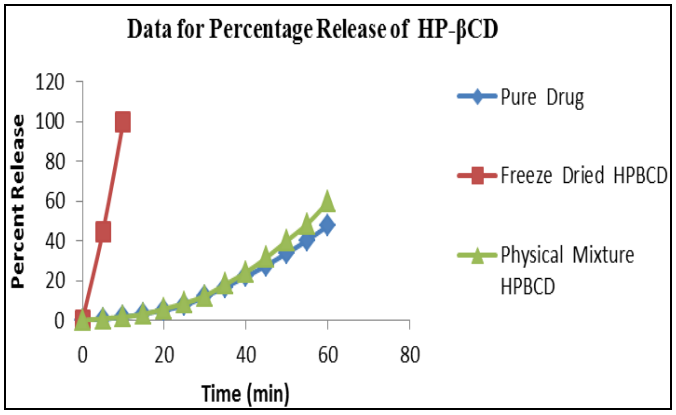

FIG. 20: PERCENTAGE DRUG RELEASE FOR HP β-CD COMPLEX

Catalepsy Study: All the observations and calculations obtained from the catalepsy model studies were subjected to ANOVA (Prism Software, Post Test Model Turkey). And results obtained for 30 mins, 60 mins and 360 mins study were found to be 99.9 % significant compared to the control. Whereas the result obtained for 120 mins was found to be 95% significant to the control group.

From the obtained results it can be predicted that there was an increase in the bioavailability of the drug when it was complexed with HPβ-CD by freeze drying technique. As there was a marked decrease in cataleptic behavior of the animals in the test group compared to the control and standard. This can be explained from **Fig. 21-24** data after 30 mins, 60mins, 120mins, and 360mins of administration of haloperidol.

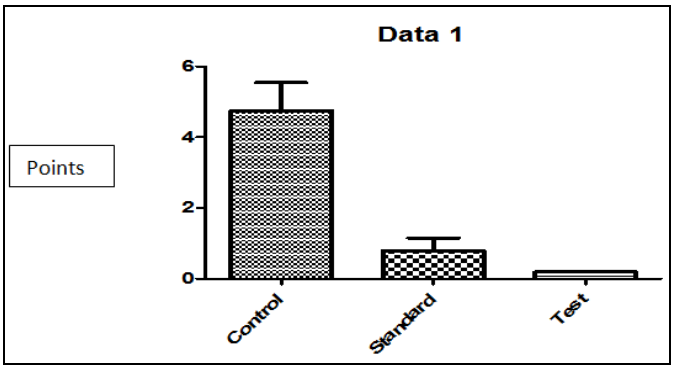

FIG. 21: DATA FOR CATALEPSY STUDY FOR 30 MIN

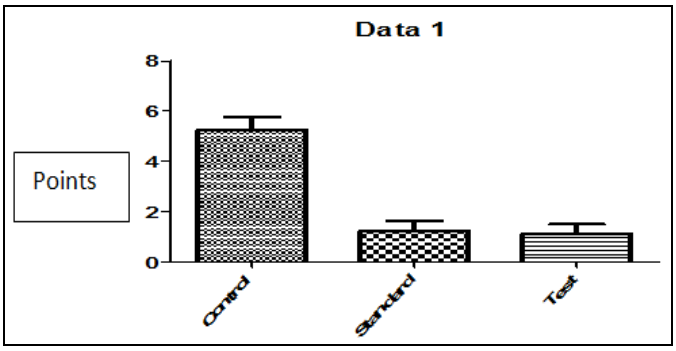

FIG. 22: DATA FOR CATALEPSY STUDY FOR 60 MIN

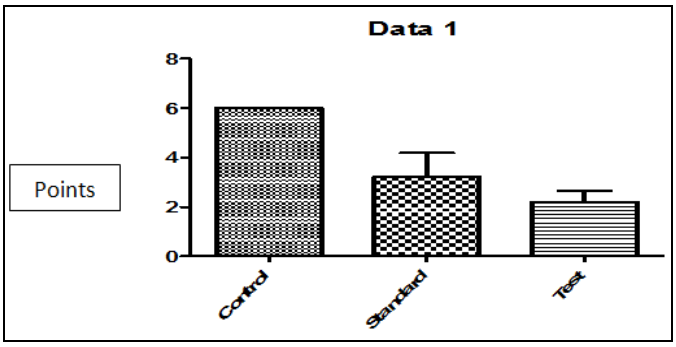

FIG. 23: DATA FOR CATALEPSY STUDY FOR 120 MIN

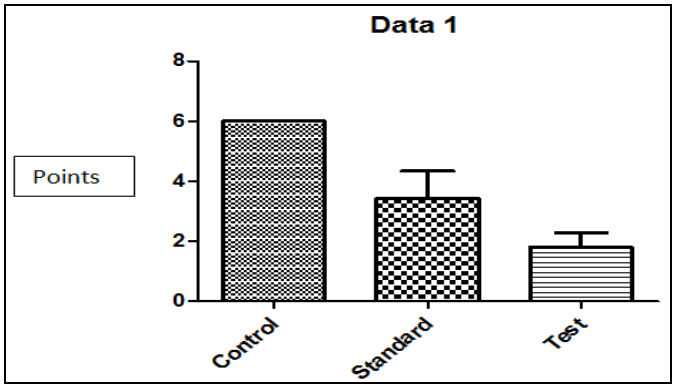

FIG. 24: DATA FOR CATALEPSY STUDY FOR 360 MIN

CONCLUSION: From the phase solubility analysis and obtained K values it was reviled that both β-CD and HP- β-CD forms 1:1 inclusion complexes with Ziprasidone HCl. The saturation solubility analysis demonstrated highest increase in the solubility of drug after complexation with HP-β-CD by lyophilisation technique. The drug content was also found to be highest in the inclusion complexes prepared with HP-β-CD by physical mixture and by freeze drying technique.

IR DSC and X-RD data reviled the complexation and conversion of drug from microcrystalline form to amorphous form and the freeze dried complexes with HP-β-CD showed 100% drug release in 10 min in *in-vitro* dissolution study performed.

Therefore the freeze dried complex with HP-β-CD was selected for Catalepsy study on Wistar rats. In the Catalepsy study the selected inclusion complex showed an increase in the bioavailability compared to the drug and almost all the data obtained from above study was found to be 99.99% significant with the control..

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CONFLICT OF INTEREST: Nil

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