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ORIGINAL ARTICLE

Effect of β-cyclodextrin complexation on physicochemical properties of zaleplon

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Abstract The physicochemical properties and dissolution profile of zaleplon (ZPN) β-cyclodextrin (βCD) inclusion complex were investigated. The phase solubility profile of ZPN with β-cyclodextrin was classified as A_L-type. Stability constant with 1:1 molar ratio was calculated from the phase solubility diagram and the aqueous solubility of ZPN was found to be enhanced by 714% ($p < 0.001$) for β-cyclodextrin. Binary systems of ZPN with βCD were prepared by kneading method. The solid-state properties of complex were characterized by differential scanning calorimetry, Fourier transformation-infrared spectroscopy and powder X-ray diffractometry. It could be concluded that ZPN could form inclusion complex with β-cyclodextrin. The dissolution profile of inclusion complex was determined and compared with those of ZPN alone and its physical mixture. The dissolution rate of ZPN was significantly increased by complexation with βCD, as compared with pure drug and physical mixture.

Keywords Zaleplon · β-Cyclodextrin · Phase solubility · Inclusion complex · Dissolution rate

Introduction

Zaleplon (ZPN) is a pyrrazolopyrimidine hypnotic drug indicated for the short term (2 to 4 weeks) management of insomnia [1]. It interacts with $GABA_A$ receptor and also shows some pharmacological properties of benzodiazepines [2]. Zaleplon also possesses potent anticonvulsant activity against pentylenetetrazole- and electroshock-induced convulsions and also causes anterograde amnesia most commonly [3]. However, the bioavailability of zaleplon is only 30% [2], which is mainly due to its low solubility (practically insoluble) in water. The very low solubility of ZPN limits its absorption from gastrointestinal tract (GIT) due to poor dissolution and this ultimately affects its oral bioavailability. Therefore attempts were made in order to enhance the solubility and dissolution profile of drug with betacyclodextrin carrier. Preparation of inclusion complex with cyclodextrins has been extensively used to improve solubility and dissolution rate of poorly water-soluble drugs [4–6]. Cyclodextrins (Fig. 1) are oligosaccharides of glucose having central hydrophobic cavity in their structure which is capable of forming stable inclusion complex with guest molecule [7]. CDs are useful carriers due to their hydrophilic nature and ability to improve the solubility of poorly water-soluble drugs, enhancement in physicochemical properties and chemical stability of drugs [8–10]. The undesired properties of drugs, such as unpleasant odour and taste can be masked with cyclodextrin inclusion complex [11]. Cyclodextrins (CDs) have gained wide acceptance in pharmaceuticals for their ability to form inclusion complex that increases the aqueous solubility and driving force for diffusion across the biological membrane for lipophilic drugs [12–15]. However, while forming inclusion complex with hydrophobic drugs, they do not alter their molecular structure and permeability characteristics [16]. Due to hydrophobic central cavities, CDs are capable of forming stable complexes with properly sized guest molecules [17]. CDs act as excellent carriers for the hydrophobic drug molecules in solution

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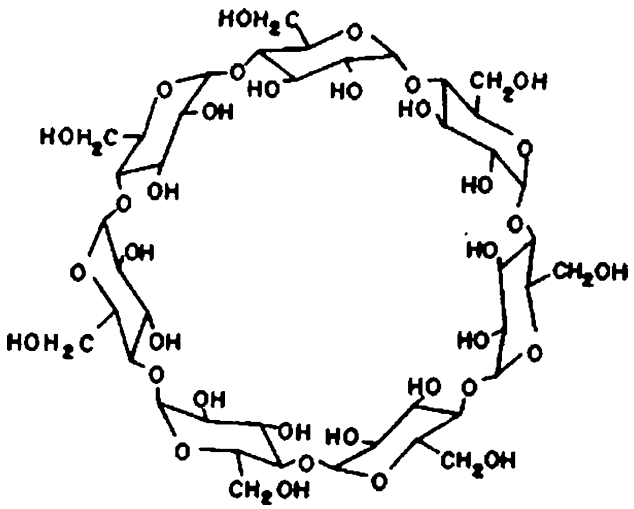

Fig. 1 β-cyclodextrin

phase and deliver them to the surface of the biological membrane [18].

The objective of the present work was to investigate the possibility of complex formation of ZPN with betacyclodextrin (βCD) in solid state and to improve its dissolution profile. The inclusion complex of ZPN with βCD was prepared by kneading method. The solubility type and the stability constant of the complex were established according to phase solubility studies. The dissolution properties of inclusion complex were studied and compared with ZPN alone and physical mixture. Differential scanning calorimetry (DSC), X-Ray powder diffractometry (XRD) and Fourier transformation-infrared spectroscopy (FTIR) were used to characterize the solid state properties of ZPN, physical mixture and inclusion complex.

Materials and methods

Materials

ZPN was kindly supplied by Cipla Ltd., Mumbai, India as a gift sample. βCD was kindly provided by Panacea Biotech, Chandigad, India. All the reagents were of analytical grade. Double distilled water was used throughout the experiment.

Phase solubility studies

Phase solubility studies were carried out in distilled water in triplicate according to the method described by Higuchi and Connors [19]. Excess amount of ZPN (50 mg) was added to 20 mL of aqueous solution containing various concentrations of βCD (0–0.01 M). Then, the suspensions were shaken on rotary shaker at 25 ± 2 °C for 4 days. After equilibrium was achieved, the samples were filtered through 0.45 μm membrane filter and appropriately diluted. The concentration of ZPN was determined spectrophotometrically (Shimadzu UV-VIS spectrophotometer 1700, Japan) at 230 nm. The apparent stability constant *K*s was calculated from phase solubility diagrams with the assumption of 1:1 stoichiometry according to the following equation:

$$K_S = \frac{slope}{S_0(1 - slope)} \quad (1)$$

S_0 is the solubility of ZPN in absence of CDs.

Preparation of solid binary systems

The following binary systems of ZPN and βCD were prepared at 1:1 molar ratio.

Preparation of physical mixture of ZPN and β-cyclodextrin

The physical mixture (PM) of ZPN and βCD in 1:1 molar ratio was prepared by mixing individual components that had previously been sieved through mesh number 60.

Preparation of inclusion complex by kneading method

ZPN and βCD with 1:1 molar ratio were accurately weighed and transferred to mortar. The mixture was then triturated in a mortar with a small volume of water-ethanol (1:1 v/v) solution till a homogenous paste was formed. The paste that formed was kneaded for 45 min and then dried at 45 °C in an oven. The dried mass was pulverized and sieved through mesh number 60.

Differential scanning calorimetry (DSC)

DSC measurements were performed on a TA SDT 2960 DSC (USA) differential scanning calorimeter. The accurately weighed sample was placed in an aluminum pan. An empty aluminum pan was used as reference. The experiment was carried out in nitrogen atmosphere (flow rate 100 mL/min) at scanning rate of 10 °C/min in the range of 0–350 °C

X-Ray powder diffractometry (XRD)

The XRD patterns of ZPN, βCD, inclusion complex, and physical mixture were recorded by using Philips Analytic X-Ray-PW 3710 (Holland) diffractometer with tube anode Cu over the interval 5–70°/2θ. The operation data were as follows: Generator tension (voltage) 40 kV, Generator current 30 mA, and scanning speed 2°/min.

Fourier transformation-infrared spectroscopy (FTIR)

Infrared spectra were obtained using a Perkin-Elmer Spectrum- one FTIR spectrometer using KBr disks. The samples were previously ground and mixed thoroughly with KBr. The KBr disks were prepared by compressing the powder. The scanning range was kept from 4000 to 450 cm^{-1}.

Saturation solubility studies

Saturation solubility studies were performed in distilled water in triplicate according to the method reported by Higuchi and Connors [19]. Excess of pure drug, physical mixture and inclusion complex were added to 20 mL of distilled water taken in stoppered conical flasks and shaken for 24 h in rotary flask shaker at room temperature. After shaking to achieve equilibrium, appropriate aliquots were withdrawn and filtered through Whatman filter paper no. 41. The filtrate so obtained was analysed spectrophotometrically at 230 nm.

Dissolution studies

The dissolution rate studies of ZPN alone, physical mixture and inclusion complex were performed in a dissolution apparatus (Model: Veego DA−6-D tablet dissolution test apparatus, Mumbai, India) using the paddle method, according to USP Type II apparatus. Dissolution studies were carried out using 900 mL of 0.1N HCl at 37 ± 0.5 °C at 75 rpm. 10 mg of ZPN or its equivalent amount of ZPN-βCD complex was added to 900 mL of 0.1N HCl. 5 mL of samples were withdrawn at time intervals of 5, 10, 15, 20, 25, 30, 45, and 60 min. The volume of dissolution medium was adjusted to 900 mL by replacing each 5 mL aliquot withdrawn with 5 mL of fresh 0.1N HCl. The solution was immediately filtered through 0.45 μm membrane filter, suitably diluted and the concentrations of ZPN in samples were determined spectrophotometrically at 230 nm.

Results and discussion

Phase solubility studies

The phase-solubility diagram for the complex formation between ZPN and βCD is presented in Fig. 2. This plot showed that the aqueous solubility of the drug increases linearly as a function of βCD. The phase solubility profile of ZPN with βCD can be classified as A_L-type. The linear host-guest correlation coefficient $r = 0.9953$ ($r^2 = 0.9905$) with a slope of 0.007922 suggested the formation of a 1:1 complex with respect to βCD concentrations. The line equation from the linear regression analysis was found to be as follows:

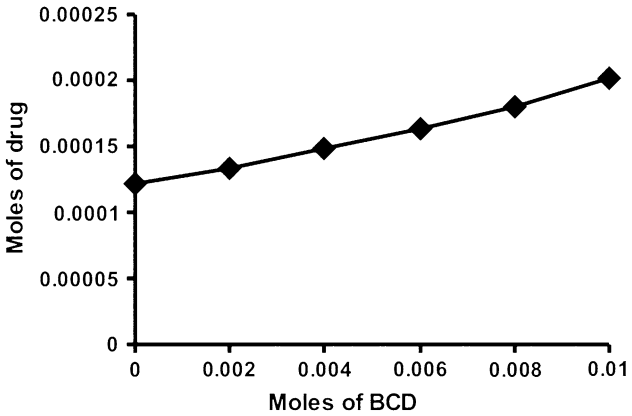

Fig. 2 Phase solubility diagram of ZPN-βCD system in water

$$y = 0.007922x + 0.0001180 \quad (2)$$

The apparent stability constant, $K_{1:1}$ obtained from the slope of the linear phase solubility diagram was 67.82 ± 1.06 M^{-1} (Eq. 1).

Differential scanning calorimetry (DSC)

The method used to identify the inclusion complex of drug with CD was differential scanning calorimetry. As observed from Fig. 3, DSC thermograms of ZPN alone (a) showed endothermic *T*max of 190.05 °C, corresponding to the melting point of crystalline form of the drug ZPN. In physical mixture (c) it is shifted to higher, with decrease in the peak intensity. For the inclusion complex (d) the peak of ZPN is shifted towards lower temperature 188.92 °C with further decrease in the peak intensity. The lower temperature of inclusion complex was because of melting point depression by the complex [20–22]. The DSC thermogram of βCD (b) showed a broad endothermic peak at 91.78 °C indicating dehydration process. The peak at 184.37 °C indicated irreversible solid-solid phase transition and the final degradation process has been shown by the broad peak at 328.66 °C. In physical mixture, the peaks of βCD shifted to 82.12 °C and 226.98 °C indicating dehydration and solid-solid phase transition respectively. The DSC thermograms for the complex showed the persistence of the endothermic peak of ZPN for the physical mixture and the kneaded product. The kneading process did not substantially affect solid-state properties of PM and complex, as the thermal behavior of kneaded ZPN and PM is similar to the untreated samples.

X-ray powder diffractometry (XRD)

The XRD pattern of ZPN showed (Fig. 4) peaks that were intense and sharp; indicating its crystalline nature (a) while XRD pattern of pure βCD is shown in Fig. 4b. Crystallinity

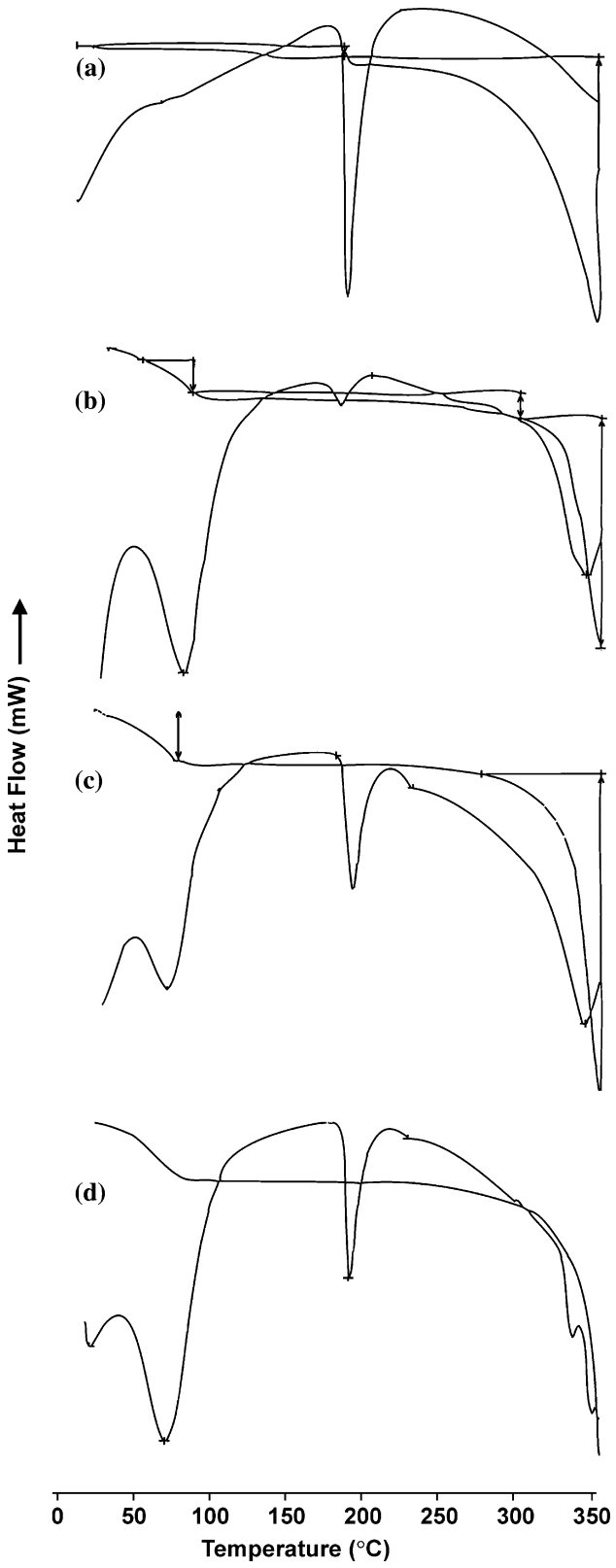

Fig. 3 DSC diagram of ZPN-βCD systems: (**a**) ZPN; (**b**) βCD; (**c**) physical mixture; (**d**) inclusion complex

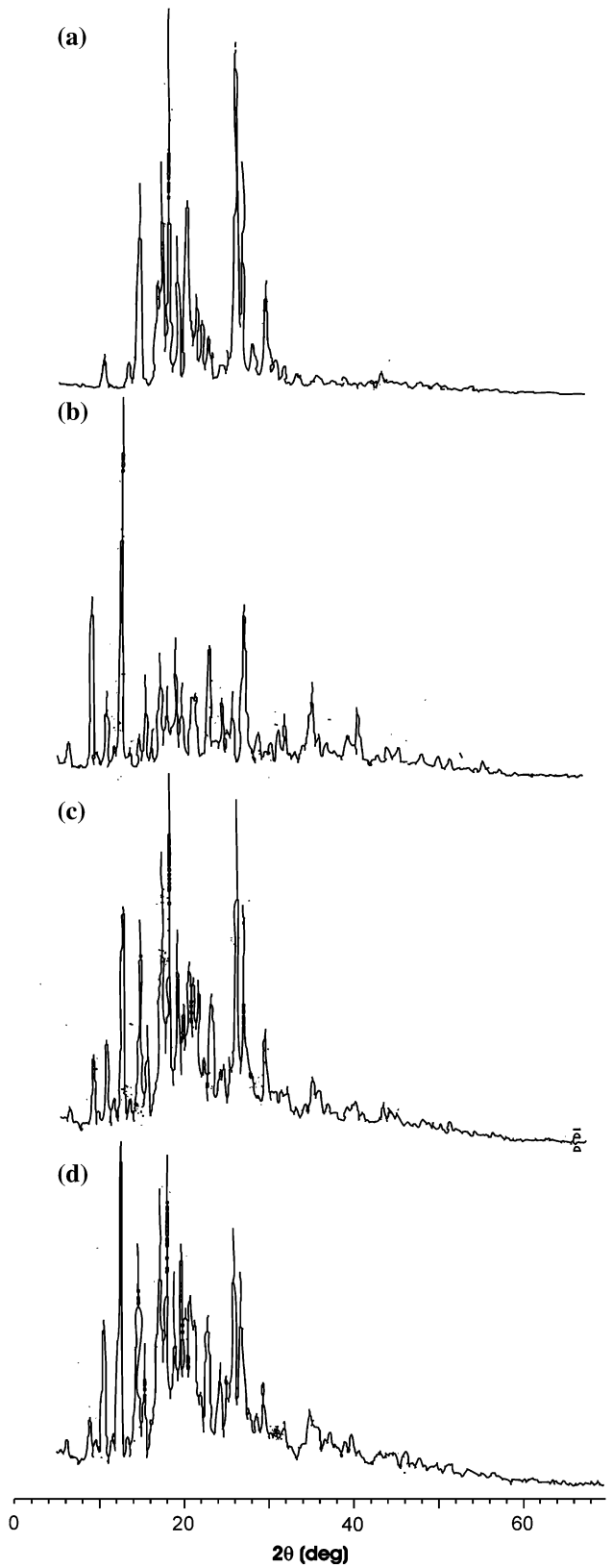

Fig. 4 XRD patterns of ZPN-βCD systems: (**a**) ZPN; (**b**) βCD; (**c**) physical mixture; (**d**) inclusion complex

was determined by comparing some representative peak heights in the diffraction patterns of the binary systems with those of a reference. ZPN showed sharp peaks at 18.01° and 25.93° (2θ) with peak intensity of 1560 and 1204 respectively. The relative degree of crystallinity (RDC) was calculated according to the equation

$$\mathrm{RDC} = \mathrm{I_{sam}}/\mathrm{I_{ref}} \quad (3)$$

where, $\mathrm{I_{sam}}$ is the peak height of the sample under investigation and $\mathrm{I_{ref}}$ is the peak height at the same angle for the reference with the highest intensity [23]. The peak height at 18.01° (2θ) was used for calculating the RDC of kneaded and physical mixture binary system. The RDC values of corresponding binary systems were 0.1480 and 0.2993, respectively. The comparative peak intensities of pure ZPN, physical mixture and kneaded product are shown in Table 1. The diffraction pattern of physical mixture (c) showed peaks of ZPN and βCD with little decrease in the peak intensity with disappearance of peak at 18.11° (2θ) of ZPN indicating reduction in crystallinity. However in kneaded system the peaks of ZPN at 14.41, 17.22 and 18.11° (2θ) were disappeared completely (d) suggesting that the crystallinity of ZPN was further reduced to a greater extent.

Fourier transformation-infrared spectroscopy (FTIR)

Figure 5 illustrates the FTIR spectra of ZPN, βCD, physical mixture and inclusion complex. IR spectrum of ZPN (a) is characterized by principal absorption peaks at 3087.98 cm^{-1} (C–H aromatic), 2928.21 cm^{-1} (C-H aliphatic), 2232.54 cm^{-1} (C$\equiv$N), 1651.53 cm^{-1} (C=O), 1614.33 cm^{-1} (C=N), 1223.35 cm^{-1} (C-N), 1576.57 cm^{-1} (C=C aromatic), 684.38 and 801.15 cm^{-1} (*m* substituted benzene). The IR spectrum of βCD (b) shows prominent peaks at 3389.64 cm^{-1} (O–H), 2924.86 cm^{-1} (C–H), 1649.90 cm^{-1} (H–O–H bending), 1157.71 cm^{-1} (C–O), 1028.51 cm^{-1} (C–O–C). The intense peaks appeared in the spectra of ZPN and βCD are due to asymmetric stretching vibrations of the functional groups. ZPN shows strong absorption peaks at 2232.54 cm^{-1} and 1651.53 cm^{-1} indicating presence of cyanide and amide carbonyl group respectively while, peaks at 684.38 and

Table 1 Peak intensities of ZPN in the XRD patterns of ZPN-βCD binary systems

2θ	Drug (ZPN)	ZPN-βCD PM	ZPN-βCD KN
14.41	729	234	–
17.22	858	388	–
18.11	942	–	–
25.93	1204	467	279
18.01	1560	467	231

PM, Physical mixture; KN, Kneaded product (complex)

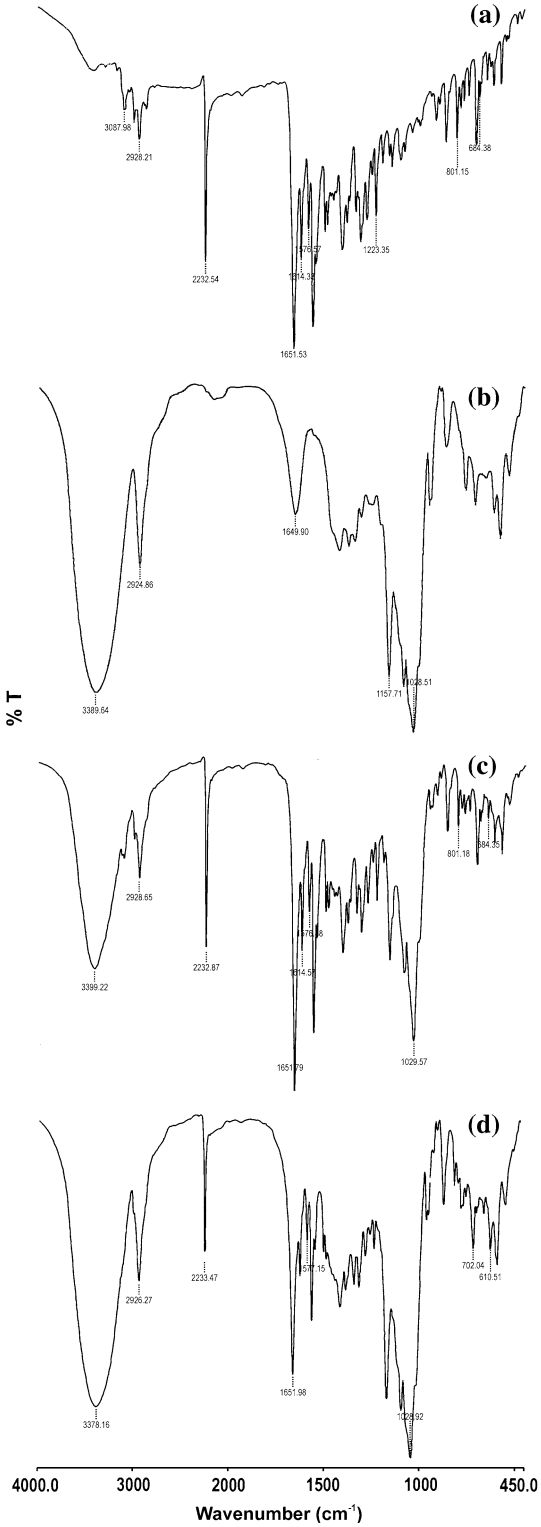

Fig. 5 FTIR spectra of ZPN-βCD systems: (**a**) ZPN; (**b**) βCD; (**c**) physical mixture; (**d**) inclusion complex

801.15 cm^{-1} may be assigned to aromatic stretching of the phenyl group in the molecule which is *m*-substituted. The IR spectrum of PM (c), shows disappearance of 3087.98 cm^{-1} and 684.38 cm^{-1} peaks of ZPN while all other peaks of

ZPN were clearly visible with slight decrease in their peak intensity. However, the peak of βCD at 3389.64 cm^{-1}, 1157.71 cm^{-1} and 1028.51 cm^{-1} were shifted to 3399.22 cm^{-1}, 1155.33 cm^{-1} and 1029.57 cm^{-1} respectively in physical mixture while the peak at 1649.90 cm^{-1} was completely disappeared. In comparison with peaks of βCD, physical mixture shows maximum peaks of pure ZPN. In IR spectra of inclusion complex (d), the peaks of ZPN at 3087.98 cm^{-1}, 2928.21 cm^{-1}, 684.38 and 801.15 cm^{-1} were found to be completely disappeared indicating that aromatic ring with amide functional group of guest has been entrapped in the hydrophobic cavity of host molecule. This has been also confirmed with a strong decrease in the peak intensity as well as shift in the peak of 1576.57–1577.15 cm^{-1} of ZPN in inclusion complex (d). Further, a slight change in the C=O group spectra (from 1651.53 to 1651.98 cm^{-1}) of ZPN was observed with strong decrease in the peak intensity in the inclusion complex (d). All other peaks of ZPN were found to be smoothened indicating strong physical interaction of ZPN with βCD. The peak of OH group of βCD at 3389.64 cm^{-1} was shifted towards lower frequency 3378.16 cm^{-1} due to intermolecular hydrogen bonding with ZPN (d). The peak at 1649.90 cm^{-1} in IR spectra of βCD due to water of crystallization, was also disappeared in both PM and inclusion complex. All the binary systems of ZPN-βCD did not show any new peaks, indicating no chemical bond formation in the complexes indicating formation of inclusion complex in solid state as shown in Fig. 6.

Saturation solubility studies

The binary systems of ZPN showed enhancement in the solubility as compared to pure drug alone. The results obtained from saturation solubility studies were statistically validated using ANOVA (Tukey-Kramer Multiple Comparisons Test) and the P values are indicated in Table 2. The

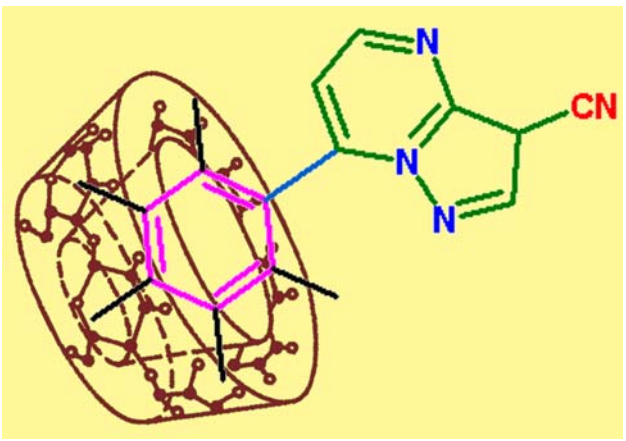

Fig. 6 Schematic representation of ZPN-βCD-inclusion complex

Table 2 Solubility data of ZPN, physical mixture (PM) and inclusion complex

System	Solubility in water at 25 °C μg/mL* (Mean ± S.D.)	S.E.M.
ZPN	42.32 ± 1.07	0.62
Physical mixture (PM)	238.71 ± 0.98[a]	0.57
ZPN-βCD complex	344.34 ± 1.07[b,c]	0.62

* Indicates mean of three experiments; S.D., standard deviation; S.E.M., Standard error of mean

[a] p value compared to pure ZPN ($p < 0.001$)

[b] p value compared to pure ZPN ($p < 0.001$)

[c] p value compared to Physical mixture (PM) ($p < 0.001$)

1:1 inclusion complex of ZPN with βCD showed higher solubility than their physical mixture and pure drug alone ($p < 0.001$). The significant enhancement in the solubility of complex is mainly attributed to the formation of stable inclusion complex of ZPN with βCD. The stability constant, 67.82 ± 1.06 M^{-1} suggests that ZPN and βCD are having sufficient affinity towards each other to form stable inclusion complex, as the solubility of complex was found to be increased by 714%. The physical mixture has also shown higher solubility than the pure drug ($p < 0.001$). The enhancement in aqueous solubility of ZPN can be explained in terms of wetting property and hydrophillicity of βCD with simultaneous reduction in the crystallinity of the drug caused by the kneading process and inclusion into the hydrophobic cavity of the βCD [24–26].

Dissolution rate studies

The dissolution curves of ZPN, physical mixture and inclusion complex in 0.1N HCl at 37 ± 0.5 °C are shown in Fig. 7. The release rate profiles were expressed as the

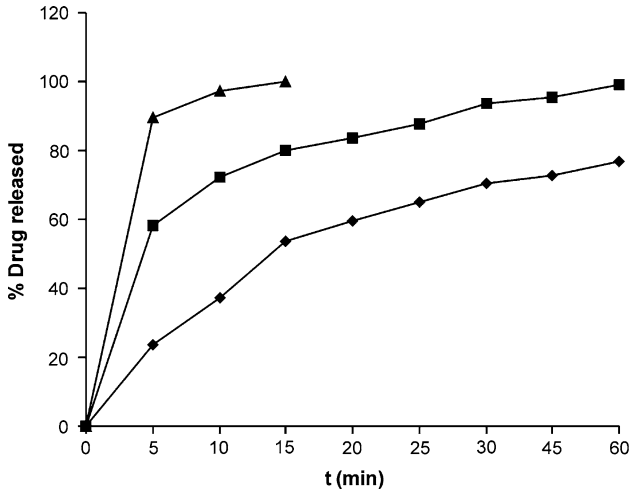

Fig. 7 The dissolution diagram of ZPN-βCD systems at 37 ± 0.5 °C: (◆) ZPN; (■) physical mixture; (▲) inclusion complex

Table 3 The dissolution time of ZPN in 0.1N HCl at 37 ± 0.5 °C

Sample source	Dissolution time (min)
ZPN	>60
Physical mixture	25.66
Inclusion complex	5.01

percentage of drug released (vs.) time. The dissolution time of ZPN from inclusion complex and physical mixture was determined and $t_{90\%}$ values are reported in Table 3 compared to ZPN alone. According to these results, the time required to release 90% drug for physical mixture was 25.66 min while inclusion complex released 90% drug within 5.01 min. However, the release of ZPN from pure drug was incomplete even in 60 min. Binary systems, PM and complex showed higher dissolution rate than the pure drug. This is because of the hydrophillicity and wetting property of βCD. The kneaded product has shown highest dissolution rate as compared to the physical mixture and pure drug, indicating complete release of ZPN from the complex. The enhancement in dissolution rate has been attributed to the formation of an inclusion complex in the solid state with reduction in the crystallinity of ZPN, as confirmed by XRD studies. The dissolution rate increase for the physical mixture and inclusion complex is due to greater hydrophillicity, higher wetting effect and ability to form stable inclusion complex of the βCD.

Conclusions

The present investigation shows that ZPN can form inclusion complex with βCD in solid state. The stoichiometry of complex formation is in 1:1 molar ratio with better stability constant. From these results, it can be assumed that the formation of the inclusion complex of ZPN with βCD can increase the aqueous solubility of ZPN. The improved dissolution rate may be due to increase in solubility, brought about by complexation. From these evidences it can be concluded that the aqueous solubility and dissolution rate of ZPN can be significantly increased by forming an inclusion complex with βCD.

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