Original Article

Proton magnetic resonance (^{1}HNMR) spectroscopy and physicochemical studies of zaleplon-hydroxypropyl-β-cyclodextrin inclusion compounds

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ABSTRACT: Proton magnetic resonance spectroscopy (^{1}HNMR) studies on inclusion compounds of zaleplon with hydroxypropyl-β-cyclodextrin (HPβCD) were carried out in order to elucidate the strength and binding mode of association. Chemical shift measurements revealed that inclusion complexes of zaleplon and HPβCD were formed by penetration of aromatic rings into the HPβCD cavity from the wider rim side with deep penetration of the amide-substituted ring while inclusion of the cyano-substituted pyrazole ring was shallow. A higher magnitude of ΔδH-3' and ΔδH-5' protons of HPβCD indicated higher stability of the lyophilized product than the kneaded one. Even from the values of ΔδH-5'/ΔδH-3', it could be concluded that zaleplon deeply penetrated inside the HPβCD cavity in the lyophilized product as compared to the kneaded product. The stoichiometry of the inclusion complexes was assessed to be a 1:1 molar ratio with an A_L-type of phase solubility curve and a stability constant of 57.89 ± 1.82 M^{-1}, according to Higuchi and Connors. In the case of dissolution experiments, a lyophilized product displayed a higher release rate of zaleplon (DE_{30}: 77.64 ± 5.74) than the kneaded complex and physical mixture.

Keywords: Zaleplon, hydroxypropyl-β-cyclodextrin, ^{1}HNMR, inclusion compounds, dissolution

1. Introduction

Molecular encapsulation *via* formation of monomolecular inclusion complexes with cyclodextrins has been extensively used in pharmaceutical research for the solubility enhancement of poorly soluble aqueous compounds (*1*). The process of molecular encapsulation involves the spatial entrapment of a single guest molecule in the cavity of the host molecule without any covalent interactions (*2,3*). Cyclodextrins have been widely employed for this purpose because of their torus shape which gives ability to entrap the hydrophobic portion of properly sized guest molecules, entirely or partially, within their hydrophobic central cavity, both in solution and in the solid state (*4*). This inclusion decreases the lipophilic character of the drug molecule with simultaneous improvement in its solubility and chemical stability (*5-9*). While forming an inclusion complex, cyclodextrins do not modify the molecular structure and permeability characteristics of hydrophobic drug molecules but deliver them to the surface of the biological membrane in their original form (*10,11*).

However, due to toxicological considerations, safety issues, and limited water solubility of parent cyclodextrins (β-cyclodextrin), some modified cyclodextrins such as 2-hydroxypropyl-β-cyclodextrin have been introduced in formulation research (*3*). 2-Hydroxypropyl-β-cyclodextrin (HPβCD) (Figure 1) is a hydroxyalkyl β-cyclodextrin derivative which is widely used in pharmaceutical formulations owing to its amorphous, non-crystalline nature, high water solubility and low toxicity (*12*). Toxicological studies revealed that HPβCD is well tolerated by the human body using both intravenous and oral administration (*13*). Therefore, an inclusion complex with HPβCD could be an effective approach to achieve ideal therapy for drugs with poor aqueous solubility (*14*).

Zaleplon selected in the current investigation is a $GABA_A$ modulating hypnotic drug belonging to the pyrrazolopyrimidine class of fused heterocyclic compounds intended for the management of insomnia (*15*). However, due to poor aqueous solubility (practically insoluble) and limited dissolution of zaleplon, only 30% of the drug reaches the systemic circulation (*16*). Because cyclodextrins can improve the solubility/dissolution of hydrophobic substances *via* complex formation (*17*), which results in improvement

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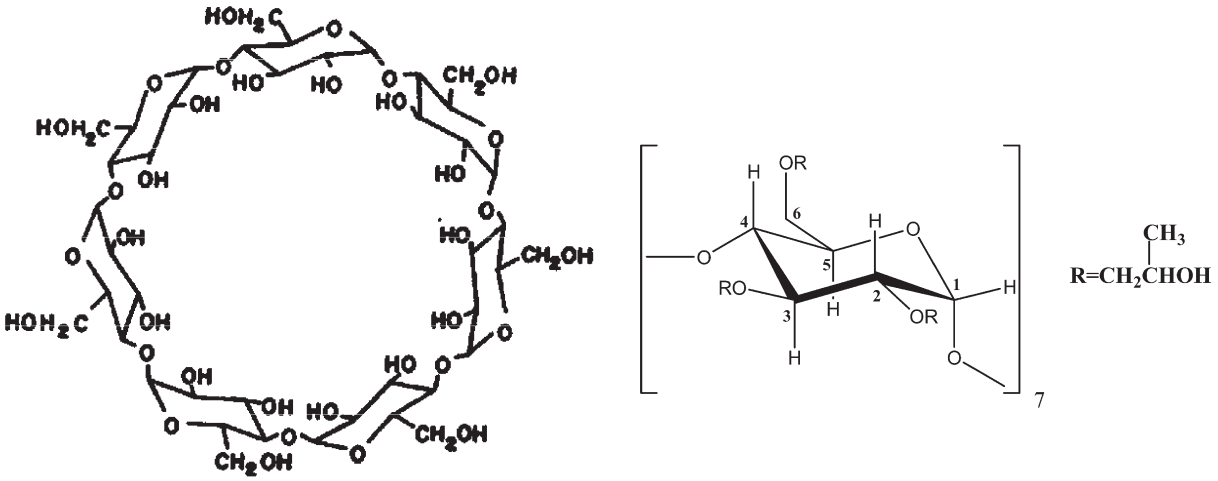

Figure 1. Hydroxypropyl-β-cyclodextrin.

of overall therapeutic effectiveness of such drugs, in this study we have used modified cyclodextrin *viz*. HPβCD to demonstrate the stability, binding mode and dissolution behaviour of zaleplon-HPβCD inclusion compounds prepared by different methods. Further, the chemically modified cyclodextrins may show different modes of arrangement of guest inside the cyclodextrin cavity due to substitution and increased cavity size. Because several papers have reported the use of the NMR technique to study the host-guest interactions during formation of inclusion complexes (*18-20*), we have employed ^{1}HNMR chemical shift measurement data to characterize zaleplon-HPβCD binary systems.

The purpose of this work was to investigate the potential of amorphous HPβCD as a solubilizing and complexing agent for zaleplon along with its binding mode with the guest. Phase solubility studies were performed to determine the stoichiometry of the complex formed in aqueous media. The inclusion compounds of zaleplon with HPβCD were prepared by a kneading and lyophilization technique while the physical mixture was prepared by mixing individual components in a mortar. All formulations including pure zaleplon were further evaluated for their dissolution performance in distilled water.

2. Materials and Methods

2.1. *Materials*

Zaleplon and HPβCD were generously provided by Cipla Ltd., Mumbai, India and Panacea Biotech, Chandigad, India, respectively. Analytical grade reagents were used for experimental purposes.

2.2. *Phase solubility studies*

Phase solubility studies in distilled water at room temperature (25 ± 2°C) were performed in triplicate according to the method of Higuchi and Connors (*21*). Excess amounts of zaleplon were added to 20 mL of aqueous solution containing various concentrations of HPβCD (0-0.01 M) in glass flasks. The glass containers were sealed and the suspensions were mechanically shaken on a rotary shaker for 4 days until equilibrium was reached. All suspensions were filtered through a 0.45 µm membrane filter and analyzed spectrophotometrically (Shimadzu UV-VIS spectrophotometer 1700, Kyoto, Japan) at 232 nm. The apparent stability constant *Ks* was estimated from the straight line of the phase solubility diagram according to the equation of Higuchi and Connors (*21*).

2.3. *Preparation of the physical mixture of zaleplon and HPβCD*

A physical mixture (PM) of equimolar amounts of zaleplon and HPβCD was prepared by homogeneous blending in a mortar of the individual components which were previously sieved through mesh number 80 µm.

2.4. *Preparation of inclusion complex by kneading method (KN)*

Kneaded products were prepared from the PM by adding a small volume of water-ethanol (1:1, v/v) solution followed by vigorously triturating it in a mortar for 45 min to form a homogeneous dispersion. The product was dried at 45°C for 24 h in an oven which was sieved through mesh number 80 µm.

2.5. *Preparation of inclusion complex by lyophilization (freeze-drying) method (LP)*

Equimolar amounts of zaleplon and HPβCD were transferred to a beaker containing distilled water and

sonicated for 20 min. The mixture was stirred for 4 days at room temperature, filtered and the resultant clear solution was frozen in a deep freezer at -20°C. The frozen solution was lyophilized in a freeze-dryer (Khera instruments, New Delhi, India) at -40°C until the sample was completely dry.

2.6. *Proton nuclear magnetic resonance spectroscopy (^{1}HNMR)*

^{1}HNMR spectra of zaleplon, HPβCD, the physical mixture and inclusion complexes were recorded in DMSO (d6) on a Varian Mercury YH-300 NMR spectrophotometer (Palo Alto, CA, USA) at an operating frequency of 300 MHz.

2.7. *Dissolution studies*

The dissolution rate studies were performed using a USP Type II dissolution test apparatus (Lab India, Model Disso 2000 Tablet dissolution test apparatus, Mumbai, India). The samples equivalent to 10 mg of zaleplon were placed in a dissolution flask containing 900 mL of distilled water maintained at 37 ± 0.5°C and stirred at 75 rpm (*22*). Samples were withdrawn at appropriate time intervals and replaced with fresh dissolution medium. After filtration through a 0.45 µm membrane filter, the concentration of zaleplon was determined spectrophotometrically at 232 nm. The results were statistically evaluated using ANOVA.

3. Results and Discussion

3.1. *Phase solubility studies*

Figure 2 shows a phase-solubility curve in aqueous media for the complex formation between zaleplon and HPβCD. It was observed that the aqueous solubility of the drug increases linearly as a function of HPβCD concentration and therefore it could be classified as A_L-type. The linear host-guest correlation coefficient r = 0.9976 (r^2 = 0.9952) with a slope of 0.05420 suggested the formation of a 1:1 complex with respect to HPβCD concentrations as the slope less than unity usually results in first order complexes. The line equation from the linear regression analysis was found to be as follows:

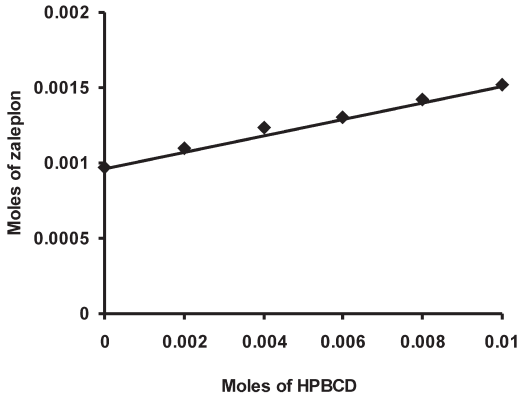

Figure 2. Phase solubility diagram of ZPN-HPβCD system in distilled water.

$$y = 0.05420\ x + 0.0009895 \qquad \text{---- Eq. 1}$$

The apparent stability constant, $K_{1:1}$ obtained from the slope of the linear phase solubility diagram was 57.89 ± 1.82 M^{-1} (Eq. 1). Thus, the stability constant of the zaleplon-HPβCD complex decreased indicating slightly less affinity of HPβCD toward zaleplon as compared to a zaleplon-βCD complex (*17*).

3.2. *Proton nuclear magnetic resonance spectroscopy (^{1}HNMR)*

Figure 3 displays ^{1}HNMR spectra of zaleplon (A), HPβCD (B), PM (C), kneaded (D), and lyophilized product (E). ^{1}HNMR spectra of zaleplon, in the absence of HPβCD, exhibited a quartet and a triplet, each integrating for three and two protons, at 3.79 and 1.15 which were assigned to H-2 and H-3, of methylene and methyl functionalities of the *N*-substituted amide group of the aromatic ring. The signal for H-1 (methyl) of the amide group of the phenyl ring appeared as a singlet at 2.104. Two doublets, each integrating for one proton, at 7.249 and 7.475 could be assigned to H-4 and H-6 protons, respectively, of the aromatic ring whereas a triplet at 7.718 was assigned to the H-5 proton of the same ring. The signals for H-7 of the phenyl ring and H-10 of the pyrazole ring appeared at 7.289 and 8.428, respectively, each as a singlet. The signals for two pyrimidine protons; H-8 and H-9 appeared at 8.006 and 8.801, respectively.

Significant changes in the nature and position of signals for the protons of zaleplon were observed in the presence of HPβCD in PM, kneaded and lyophilized products. The signals for H-1, H-2, H-3, and H-5 protons of the aromatic ring including the amide group, exhibited upfield shifts in all binary systems of zaleplon with HPβCD whereas the signals for H-4, H-6, and H-7 of the aromatic protons exhibited downfield shifts in the PM and kneaded system. Two pyrimidine protons; H-8 and H-9 also experienced downfield shifts in all binary systems of zaleplon while a signal for the H-10 of the pyrazole ring exhibited an upfield shift. The protons H-8 and H-10 were almost diffused in the lyophilized product. However, all aromatic ring protons including protons of the amide group experienced high upfield shifts in the lyophilized system indicating formation of an inclusion complex. The physical mixture and kneaded system displayed a similar shifting pattern of zaleplon protons. The chemical shift change values for

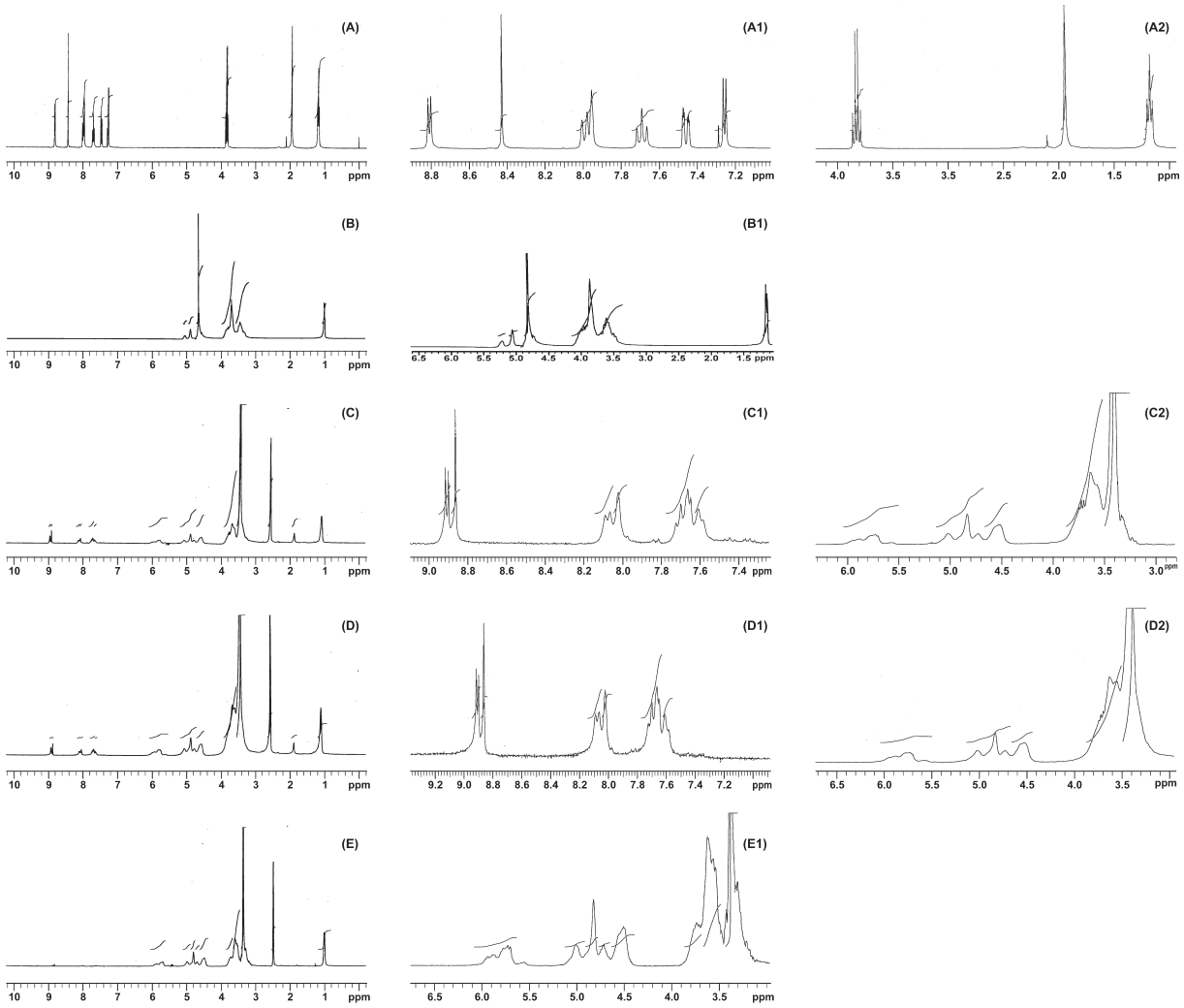

Figure 3. ^{1}HNMR spectra of ZPN-HPβCD binary systems. A, A1, and A2, ZPN; B and B1, HPβCD; C, C1, and C2, physical mixture; D, D1, and D2, kneaded product; E and E1, lyophilized product.

Table 1. ^{1}HNMR (300 MHz) chemical shift change (Δδ) values for various protons of ZPN in the presence of HPβCD in DMSO

System/Protons	PM	KN	LP
H-1	-0.290	-0.291	-1.076
H-2	-1.290	-1.290	-1.288
H-3	-0.123	-0.122	-0.141
H-4	0.359	0.362	-1.547
H-5	-0.021	-0.020	-1.778
H-6	0.187	0.187	-1.601
H-7	0.357	0.359	-1.558
H-8	0.015	0.015	---
H-9	0.060	0.061	0.063
H-10	-0.365	-0.363	---

Negative values indicate upfield shift. PM, physical mixture; KN, kneaded product; LP, lyophilized product.

Table 2. ^{1}HNMR (300 MHz) chemical shift change (Δδ) data for HPβCD protons in the presence of ZPN in DMSO

System/Protons	H-3'	H-5'	ΔδH-5'/ΔδH-3'
KN	-0.098	-0.144	1.50
LP	-0.106	-0.233	2.19

Negative values indicate upfield shift. KN: kneaded product; LP: lyophilized product.

various protons of the guest are given in Table 1.

In the NMR spectra of kneaded and lyophilized systems, the signals for H-5' and H-3' protons of HPβCD, situated inside the HPβCD cavity, exhibited high upfield shifts compared to pure HPβCD whereas, in PM, H-5' and H-3' protons of HPβCD, moved downfield by 0.011 (ΔδH-5') and 0.004 (ΔδH-3'), respectively. The chemical shift change (Δδ) values for HPβCD protons in the kneaded and lyophilized systems are given in Table 2.

The mode of the guest complex into the host cavity of cyclodextrins involves the insertion of the less polar (non-polar) portion of the guest into the CD cavity as reported in earlier papers (*4*). NMR spectroscopy is an excellent tool for the study of the nature and geometry of the cyclodextrin inclusion complex due to its high sensitivity (*23*). The penetration of guest usually takes

place from the wider rim side of the cavity. The host-guest interactions are clearly reflected in the form of shifts in NMR signals. The changes in chemical shifts of H-3' and H-5' protons of HPβCD in the presence of the guest molecule indicated that the inclusion in the cavity has taken place in the kneaded and lyophilized systems since these protons are located inside the cavity (*24*). A deep penetration of guest into the HPβCD cavity results in the chemical shift of both protons H-3' and H-5' of HPβCD whereas the shift in only H-3' protons occurs when the cavity penetration is shallow (*25*). The ratio for the chemical shift changes for these protons, ΔδH-5'/ΔδH-3', gives information about the depth of inclusion of the guest into the HPβCD cavity which was found to be higher in the lyophilized system than the kneaded one (Table 2). On the contrary, in the PM, H-3' and H-5' protons of HPβCD exhibited downfield shifts indicating no formation of an inclusion complex, even though the protons of zaleplon have shown similar behaviour in the PM and kneaded system. These results suggested an existence of a strong physical interaction between zaleplon and HPβCD in the PM. The stability of inclusion complex is related to the magnitude of the chemical shift changes for H-3' and H-5' protons; the higher the value of ΔδH-3' and ΔδH-5', the greater is the stability of the complex (*26*). The protons of the guest molecule located inside the HPβCD cavity in complex, experience upfield shift changes due to the shielding effect by the cavity while, the protons of the guest, which are outside the cavity, show downfield shift changes when complexed (*24*). Significant high field shifts observed in the NMR signals of H-3' and H-5' of HPβCD in kneaded and lyophilized systems of zaleplon clearly indicated the inclusion of the aromatic part of the guest into the HPβCD cavity due to hydrophobic interactions (*27*). The higher values of ΔδH-5' and ΔδH-3' protons of HPβCD might be attributed to the deep penetration of the zaleplon from the wider rim of HPβCD (*28*). Further, almost all protons of the aromatic ring, including the protons of the amide group, exhibited significant upfield shifts in kneaded and lyophilized products indicating its penetration inside the HPβCD cavity. However, the H-10 proton of cyano substituted pyrazole ring has also experienced a remarkable upfield shift in kneaded but is diffused in the lyophilized system, which may indicate the possibility of penetration of the cyano substituted pyrazole ring inside the HPβCD cavity. This interpretation has been supported by the loss of intensity and disappearance of the cyanide peak in IR spectra of kneaded and lyophilized products respectively (data not shown). Therefore, two different topologies of complex formation could be possible for each aromatic ring as entry may occur through either the wider or smaller rim of HPβCD, resulting in either shallow or deep penetration of the guest molecule. Figure 4 illustrates possible models of inclusion equilibria of the zaleplon and HPβCD inclusion complex. The ΔδH values obtained in NMR signals of kneaded and lyophilized products supports the possible model-1 for the amide-substituted aromatic ring with HPβCD where, the zaleplon enters from the wider rim and penetrates deep so that the amide group protrudes outside the cavity and may interact with 2'-OH of HPβCD at the 6 position. Further evidence was seen in the upfield shift of H-4 and H-5 of zaleplon in the lyophilized product. This might be because of the close proximity of these protons with H-5' while the H-5 and H-6 of zaleplon were in the proximity of both H-3' and H-5' of HPβCD, since these protons have experienced higher upfield shifts than H-4 and H-5 in the lyophilized system. The high upfield shift of H-10 of the cyano substituted pyrazole ring in the kneaded system suggests the possible model-2 indicating the possibility of penetration of the cyano substituted pyrazole ring from the narrow side where only a part of the ring enters the cavity with shallow cavity penetration. Thus ^{1}HNMR measurements are clearly indicative of formation of inclusion compounds in the solid state.

3.3. *Dissolution rate studies*

Figure 5 shows dissolution curves of the zaleplon-HPβCD binary systems in distilled water. As shown in Table 3, the values of % drug dissolved at 2 min (DP_2), 15 min (DP_{15}), 30 min (DP_{30}), and dissolution efficiency (*29*) at 30 min (DE_{30}) were evaluated.

From the results obtained, it was observed that all binary systems of zaleplon with HPβCD show faster dissolution than zaleplon alone. It should be noted that the increase in dissolution rate of zaleplon was 2.04-fold greater from the physical mixture within 2 min whereas, it was 2.96-fold greater from the kneaded system at the

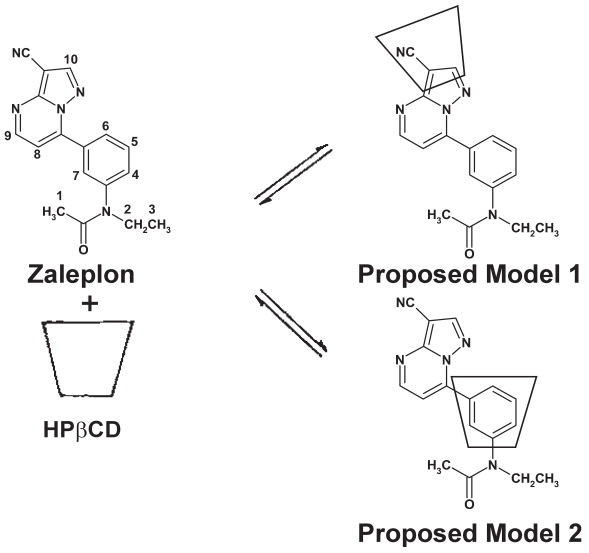

Figure 4. A schematic representation of the inclusion equilibria of ZPN with HPβCD.

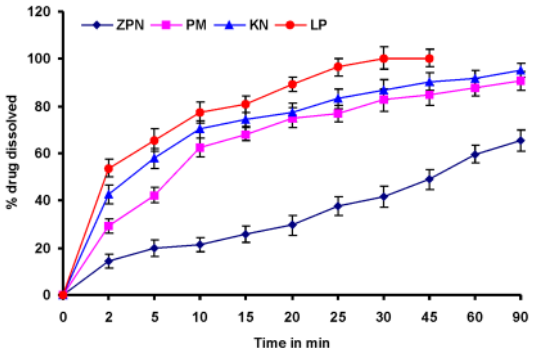

Figure 5. The dissolution curves of ZPN-HPβCD system in distilled water at 37°C ± 0.5°C. ZPN, zaleplon; PM, physical mixture; KN, kneaded product; LP, lyophilized product.

Table 3. The dissolution data of pure ZPN and its various binary systems with HPβCD in distilled water

System[a]	DP_2 ± S.D.[b]	DP_{15} ± S.D.[b]	DP_{30} ± S.D.[b]	DE_{30} ± S.D.[b]
ZPN	14.34 ± 3.1	25.76 ± 3.6	41.63 ± 4.5	26.27 ± 3.58
PM	29.32 ± 2.9	68.13 ± 2.8	82.63 ± 4.7	62.06 ± 3.49[c]
KN	42.55 ± 3.9	74.25 ± 2.9	87.02 ± 4.3	69.08 ± 3.56[c]
LP	53.59 ± 3.7	80.63 ± 3.5	100.32 ± 4.6	77.64 ± 5.74[c,d]

[a] ZPN, zaleplon; PM, physical mixture; KN, kneaded product; LP, lyophilized product; [b] DP and DE indicate % drug dissolved and % dissolution efficiency, respectively (mean ± standard deviation, n = 3); [c] p value compared to pure ZPN ($p < 0.001$); *i.e.,* all significant; [d] p value compared to PM ($p < 0.01$); *i.e.,* significant.

same time. The lyophilized product displayed a higher dissolution rate than the physical mixture and kneaded product. The increase in dissolution rate of zaleplon was 3.73-fold greater from lyophilized product within 2 min.

The statistical treatment (ANOVA) of DE_{30} values of zaleplon and its formulations demonstrated a significant difference between the dissolution profile of pure zaleplon and all of its binary systems with HPβCD ($p < 0.001$). Further, lyophilized product has shown significant improvement in the dissolution profile of zaleplon than the physical mixture ($p < 0.01$). However, no significant difference was observed between the dissolution profiles of physical mixture and kneaded product. Similar results were obtained with the kneaded and lyophilized products. However, the lyophilized product has shown excellent dissolution among all other binary systems of zaleplon studied.

It is noteworthy that the extent of the dissolution enhancing effect was dependent on the method used for the preparation of inclusion complexes. The enhancement in dissolution rate from the physical mixture was possibly due to a local solubilization action and improved wettability by HPβCD and hence dissolution of the drug particles (*30,31*).

The kneaded product has shown a dissolution rate between the physical mixture and lyophilized product. The higher dissolution rate of kneaded product compared to physical mixture might be because of reduction in crystals (XRD data not shown) of the drug due to formation of the inclusion complex (kneaded product) in the solid state.

A significant increment in dissolution rate of zaleplon from lyophilized product could be attributed to loss of crystallinity or probably transfer of zaleplon into a higher energetic amorphous state upon complex formation, surfactant-like properties of HPβCD (*32-35*) and higher stability of inclusion complex in lyophilized product (*36*).

In conclusion, the dissolution rate of zaleplon could be increased by formation of its inclusion compounds with hydrophilic and amorphous HPβCD by a kneaded and lyophilized process.

4. Conclusion

In the present investigation, ^{1}HNMR shifts of zaleplon in the presence of HPβCD confirmed the formation of equimolar zaleplon-HPβCD inclusion compounds in the solid state prepared by kneading and lyophilized techniques. Both, the amide-substituted phenyl ring (deep penetration) and cyano-substituted pyrazole ring (shallow penetration) act as guests. In all aspects, a lyophilized product was found to be more stable than a kneaded one. The stoichiometry of complex formation was 1:1 as supported by phase solubility studies. The results obtained from dissolution studies show a high potential for HPβCD as a solubilizing and complexing agent for zaleplon which should be useful for improvement of oral bioavailability of zaleplon.

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