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Preparation and characterization of inclusion complexes of prazosin hydrochloride with β-cyclodextrin and hydroxypropyl-β-cyclodextrin

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Abstract

The slightly water-soluble drug prazosin hydrochloride (PRH) and its inclusion with either β-cyclodextrin (βCD) or hydroxypropyl-β-cyclodextrin (HPβCD) were investigated. The phase solubility profiles of PRH with βCD and HPβCD were classified as B_s- and A_L-types, respectively. Stability constants with 1:1 molar ratio were calculated from the phase solubility diagrams and the solubility of PRH could be enhanced by 27.6% for βCD and 226.4% for HPβCD, respectively. Binary systems of PRH with βCD or HPβCD prepared by various methods were characterized by differential scanning calorimetry and Fourier transformation-infrared spectroscopy. It could be concluded that PRH could form inclusion complex with either βCD or HPβCD. The dissolution profiles of inclusion complexes were determined and compared with those of PRH alone and their physical mixtures. The dissolution rate of PRH was increased by βCD and HPβCD inclusion complexation remarkably. Both the preparation technique and nature of the carriers played important roles in the dissolution performance of the systems. All the systems with HPβCD showed better performance than the corresponding ones with βCD.

Keywords: Prazosin hydrochloride; β-Cyclodextrin; Hydroxypropyl-β-cyclodextrin; Inclusion complex; Phase solubility; Dissolution rate

1. Introduction

Prazosin hydrochloride (PRH), 1-(4-amino-6,7-dimethoxy-2-quinazolinyl)-4-(2-furanylcarbonyl) piperazine HCl (Fig. 1), a selective α_1-adrenoceptor antagonist in clinical use [1–3], has gained a widespread acceptance in the management of hypertension and in the treatment of congestive heart failure [4,5]. However, the bioavailability of PRH is very low, which is mainly due to its low solubility in water. Therefore, it is very important to introduce effective methods to enhance the solubility and dissolution rate of PRH.

Complexation with cyclodextrins has been widely used to improve the solubility and dissolution rate of poorly water-soluble drugs [6–8]. Cyclodextrins (CDs) are macrocyclic oligosaccharides with six to eight D-glucose units called α-cyclodextrin, β-cyclodextrin (βCD) and γ-cyclodextrin, respectively. The most important structural feature of CDs is that they have hydrophobic central cavities capable of forming stable complexes with properly sized drug molecules [9–11]. CDs have attracted the attention of many formulation experts due to their improvement in solubility of poorly water-soluble drugs, enhancement in physical and chemical stability of drugs [12] and elimination of the undesired properties of drugs, such as unpleasant odour and taste [13]. Among these CDs, βCD and its hydrophilic derivative, such as hydroxypropyl-β-cyclodextrin (HPβCD) are the first choices because of their suitable cavity sizes and low price.

The aims of the present paper are to investigate the possibility of complex formation of PRH with βCD and its derivative HPβCD in solution and in solid state and to select a suitable complex, which is a crucial step in the development of PRH formulation. The inclusion complexes of PRH with βCD or HPβCD were prepared by various methods, i.e.,

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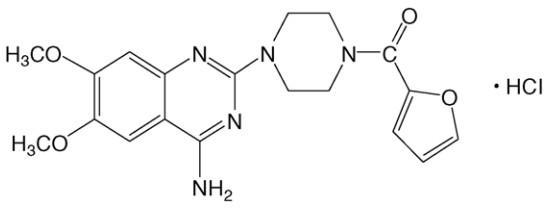

Fig. 1. Chemical structure of prazosin hydrochloride.

grinding, ultrasonic method and co-precipitation. The types and the stability constants of the complexation were established according to phase solubility studies. The dissolution properties of inclusion complexes were evaluated compared with those of PRH alone and the corresponding physical mixtures. Differential scanning calorimetry (DSC) and Fourier transformation-infrared spectroscopy (FTIR) were used to characterize the solid states of all the binary systems.

2. Materials and methods

2.1. Materials

PRH (M_r = 420) was obtained from Songsheng Institute and Plant of Pharmaceutical and Chemical (Jiangsu, China), βCD (M_r = 1135) from Shanghai Bio Life Science and Technology Co. Ltd. (Shanghai, China) and HPβCD (M_r = 1402, degree of molar substitution 0.66) from Yiming Fine Chemicals Co. Ltd. (Jiangsu, China). All the regents were of analytical grade. Distilled water was used all through the experiment.

2.2. Preparation of binary systems of PRH–cyclodextrin

The binary systems of PRH–βCD and PRH–HPβCD were prepared in various methods, i.e., grinding, ultrasonic method and co-precipitation. The physical mixtures were also prepared for the purpose of comparison.

2.2.1. Preparation of inclusion complexes by grinding

PRH and CDs with 1:1 molar ratio were accurately weighed. A homogenous paste was prepared by mixing CD and a small amount of water in a mortar. Then, PRH was added. The paste was further ground for 30 min. The obtained masses were dried at 40 °C in an oven for 24 h. The dried complexes were ground to fine powder and screened through 80-mesh sieve.

2.2.2. Preparation of inclusion complexes by ultrasonic method

PRH and CDs with 1:1 molar ratio were accurately weighed. A saturated CD solution was prepared with CD and water. After the addition of PRH, a suspension was formed. Then, the suspension was stirred in an ultrasonic machine for 6 h. The following process was the same as the grinding method.

2.2.3. Preparation of inclusion complexes by co-precipitation

PRH and CDs with 1:1 molar ratio were accurately weighed. Saturated CD solutions were prepared with CDs and water. Then, PRH solution in methanol was added slowly and a suspension was formed. The suspension was stirred at 40 °C for 30 min and kept stirring at room temperature for 24 h. The obtained masses were filtered through 0.45 μm membrane filter and dried at 40 °C in an oven for 24 h. The dried complexes were ground to fine powder and screened through 80-mesh sieve.

2.2.4. Physical mixtures of PRH and CDs

Physical mixtures were prepared by simply blending PRH and CDs with 1:1 molar ratio uniformly in a mortar.

2.3. Phase solubility studies

Phase solubility studies were carried out in water according to the method described by Higuchi and Connors [14]. In brief, excess amount of PRH (40 mg) was added to 10 ml of aqueous solution containing various concentrations of βCD (0–0.016 M) or HPβCD (0–0.1 M). Then, the suspensions were shaken at 25 ± 2 °C for 7 days. After equilibrium attainment, the samples were filtered through 0.45 μm membranes filter and properly diluted. The concentration of PRH was determined spectrophotometrically (S52, China) at 246 nm [15]. The apparent stability constants K_s were calculated from phase solubility diagrams with the assumption of 1:1 stoichiometry according to the following equation:

$$K_s = \frac{\text{slope}}{S_0\,(1 - \text{slope})} \quad (1)$$

S_0 is the solubility of PRH in the absence of CDs.

2.4. DSC

DSC measurements were performed by a Perkin-Elmer DSC7 differential scanning calorimeter with a Pyris Series Workstation (Perkin-Elmer, USA). The accurately weighed sample was placed in an aluminum pan and an empty aluminum pan was used as reference. The experiment was carried out under nitrogen flow (20 ml/min) at scanning rate of 10 °C/min in the range of 50–300 °C.

2.5. FTIR spectroscopy

Infrared spectra were obtained using a Shimadzu FTIR-8900 spectrometer (Shimadzu, Japan). The samples were previously ground and mixed thoroughly with KBr, an infrared transparent matrix. The KBr disks were prepared by compressing the powder. The scans were executed at a resolution of 8 cm^{-1} (from 4000 to 400 cm^{-1}).

2.6. Dissolution rate studies

The dissolution rate studies of PRH, alone and from various PRH–cyclodextrin systems, were conducted in a dissolution apparatus (RCZ-8A, China) using the paddle method, according to USP XXVI at 37 ± 0.5 °C, stirring at 50 r/min. 10 mg of PRH or its equivalent amount of PRH–cyclodextrin was added to 100 ml of water; 5 ml of solution was taken out and replaced with the same volume of fresh medium in 1, 2, 4, 6, 8, 12, 16 and 30 min, respectively. The solution was immediately filtered through 0.45 μm membrane filter, suitably diluted and determined spectrophotometrically at 246 nm.

3. Results and discussion

3.1. Preparation of solid binary systems

The yields of the products were different due to different processes, which were 88.6% for grinding, 88.4% for ultrasonic method and 80.8% for co-precipitation.

3.2. Phase solubility

The phase solubility profiles of PRH–βCD and PRH–HPβCD are presented in Figs. 2 and 3, respectively. The phase solubility diagram of PRH–βCD could be classified as B_S-type according to Higuchi and Connors. The solubility of PRH increased with the increasing of concentration of βCD in the range of 0–8 mM. When the concentration of βCD was more than 8 mM, it led to the formation of an insoluble substance [16]. The molar ratio of the inclusion complex was achieved from the initial ascending part of the curve, a nearly straight line with a slope of 0.084 (r = 0.9919), which

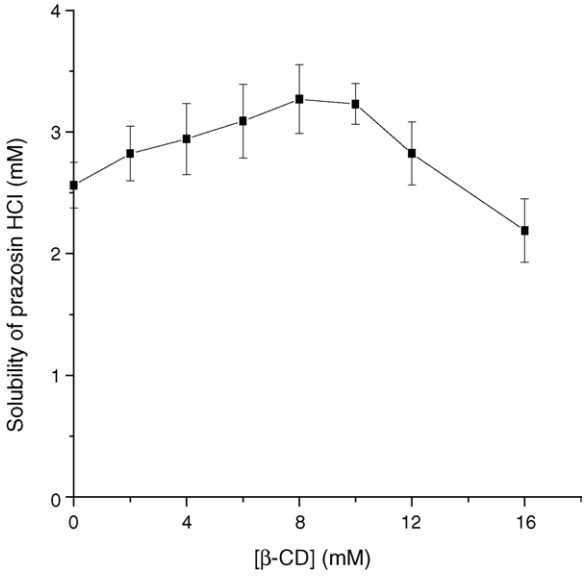

Fig. 2. Phase solubility diagram of PRH–βCD system in water.

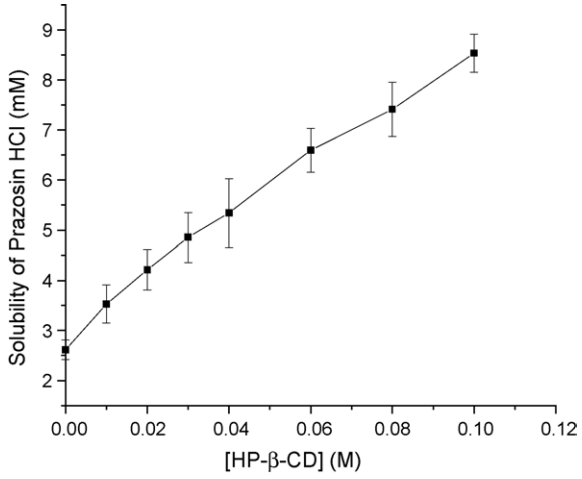

Fig. 3. Phase solubility diagram of PRH–HPβCD system in water.

indicated that a complex with 1:1 molar ratio was formed in the solution. The apparent stability constant, $K_{1:1}$, was obtained to be 29.7 ± 2.5 M^{-1} according to Eq. (1). While the phase solubility diagram of PRH–HPβCD was significantly different from that of PRH–βCD and the curve followed an A_L-system, which showed a linear increase of PRH solubility as a function of HPβCD concentration with a slope of 0.060 (r = 0.9958) during the concentration range investigated. The $K_{1:1}$ was obtained to be 20.8 ± 2.9 M^{-1}.

The $K_{1:1}$ value showed that PRH formed more stable complexes with βCD than with HPβCD, which may be due to a steric hindrance of hydroxypropyl of HPβCD, which prevented the guest molecule from entering the CD cavity.

At the CD concentration of 8 mM, the solubility of PRH was increased by 27.6% for βCD and by 23.8% for HPβCD, respectively. It was the best improvement for PRH solubility in this concentration level of βCD. In the case of HPβCD, due to its higher solubility, larger amount could be used to improve the solubility of PRH. 226.4% enhancement of PRH solubility could be achieved in the concentration of 100 mM HPβCD.

3.3. DSC analysis

DSC can be used for the recognition of inclusion complexes. When guest molecules were embedded in CD cavities or in the crystal lattice, their melting, boiling or sublimation points generally shifted to a different temperature or disappeared [17]. The thermograms of PRH and the binary systems are shown in Figs. 4 (PRH–βCD) and 5 (PRH–HPβCD).

The DSC diagram of PRH (Fig. 4a) exhibited a sharp endothermic peak at 282.3 °C, indicating the melting point of PRH. The trace of βCD (Fig. 4b) showed a very broad endothermic effect, between 60 and 110 °C, which attained a maximum around 90 °C, corresponding to dehydration process, followed by an irreversible solid–solid phase transition at 214 °C and finally, to a degradation process, which took place at around 300 °C [18]. For the physical mixture of PRH

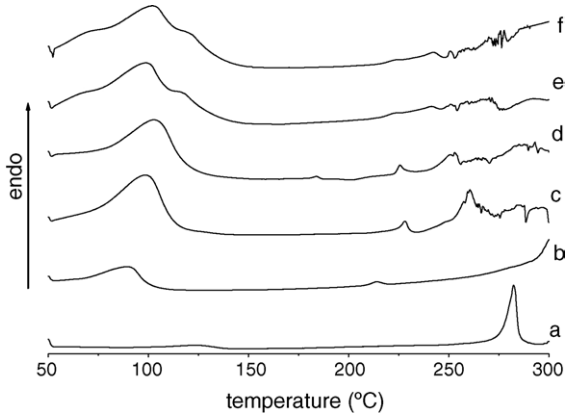

Fig. 4. DSC diagram of PRH–βCD systems: (a) PRH; (b) βCD; (c) physical mixture; (d) inclusion complex by grinding; (e) inclusion complex by ultrasonic method; (f) inclusion complex by co-precipitation.

and βCD (Fig. 4c), the drug endothermic peak shifted from 282.3 to 260.6 °C and the peak of βCD at 214–228.2 °C. For the inclusion complexes prepared by grinding (Fig. 4d), it showed similar DSC profile with physical mixture, in which the drug endothermic peak and βCD peak mentioned above shifted to 253.0 and 225.6 °C, respectively. It should be difficult to form inclusion complex when both PRH and βCD were in solid state. While turning to the inclusion complexes prepared by ultrasonic method and co-precipitation (Fig. 4e and f), there was only dehydrated peak of βCD, the endothermic peak of PRH at 282.3 °C disappeared. These results indicated the existence of interactions between PRH and βCD by ultrasonic method and co-precipitation to form inclusion complexes.

The thermogram of HPβCD (Fig. 5b) exhibited a very broad endothermic peak between 60 and 100 °C (maximum at 62 °C), corresponding to release of water molecules. The

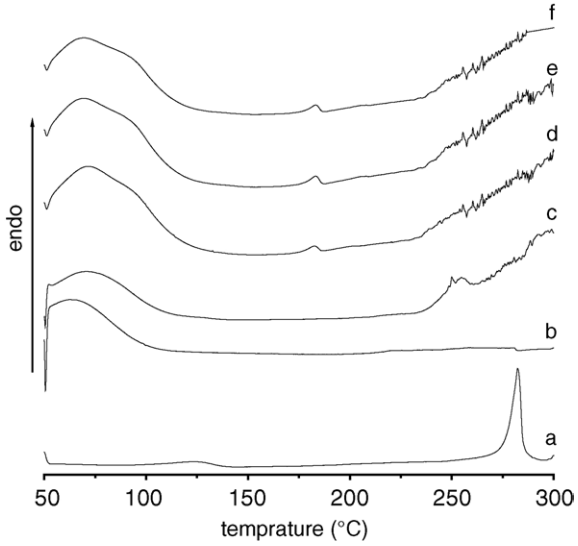

Fig. 5. DSC diagram of PRH–HPβCD systems: (a) PRH; (b) HPβCD; (c) physical mixture; (d) inclusion complex by grinding; (e) inclusion complex by ultrasonic method; (f) inclusion complex by co-precipitation.

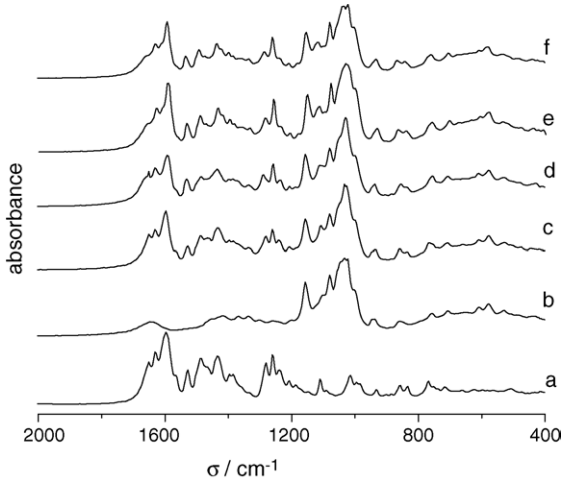

Fig. 6. FTIR spectra of PRH–βCD systems: (a) PRH; (b) βCD; (c) physical mixture; (d) inclusion complex by grinding; (e) inclusion complex by ultrasonic method; (f) inclusion complex by co-precipitation.

trace of physical mixture (Fig. 5c) showed the drug melting endotherm, which shifted to lower temperature and more or less broadened and reduced in intensity. Concerning the thermal curves of inclusion complexes of PRH with HPβCD prepared by three different methods (Fig. 5d–f), the endothermic peak of PRH at 282.3 °C disappeared but presented a new peak at 180 °C with reduced in intensity as a consequence of interaction between the components.

3.4. FTIR spectroscopy

Inclusion complexes were also analyzed using FTIR spectroscopy. The FTIR spectra of wave number from 2000 to 400 cm^{-1} are presented in Figs. 6 (PRH–βCD) and 7 (PRH–HPβCD).

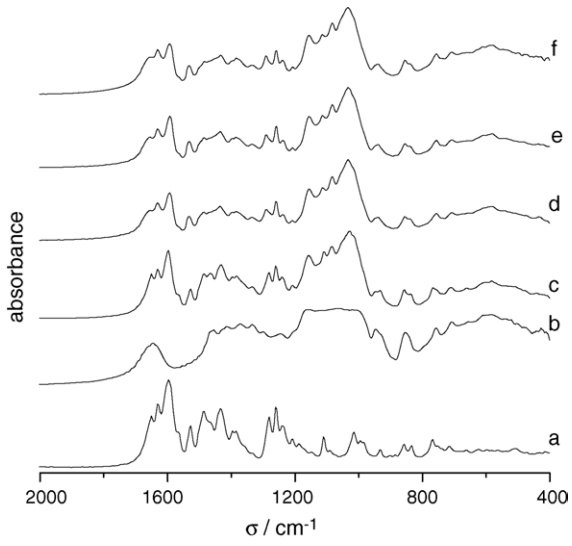

Fig. 7. FTIR spectra of PRH–HPβCD systems: (a) PRH; (b) HPβCD; (c) physical mixture; (d) inclusion complex by grinding; (e) inclusion complex by ultrasonic method; (f) inclusion complex by co-precipitation.

PRH showed a very strong absorption bands between 1720 and 1560 cm^{-1} for carbonyl stretching band, which split into triplet (the absorption peak showed in 1650, 1631 and 1593 cm^{-1}, respectively) due to the influence of atom N and the furan ring attached to C=O: 1261 and 1434 cm^{-1} for ether absorption band of ph–O–C and C–H in the aromatic ring; 1527 cm^{-1} was denoted for stretching vibration of C=C in the aromatic ring. All the binary systems of PRH–CD did not show any new peaks, indicating no chemical bonds created in the formed complexes.

The main characteristic triplet appeared also at the same position in the physical mixtures with both CDs and co-ground product with βCD in accordance with the thermal analysis results. However, the spectra of binary system of PRH–HPβCD obtained by grinding and inclusion complexes prepared by ultrasonic method and co-precipitation with both CDs, whose bands changed to doublet with peak in 1650 cm^{-1} disappeared, suggested that the carbonyl group of PRH was entrapped into the host cavities, during inclusion complexation. Other bands, such as 1527 cm^{-1} suffered a slight shift, probably due to the influence of overlapping with the CDs in the same zone, which perturbs the energy of these vibrations. There were slight differences between binary systems with two kinds of carriers, the wave number of 1527 cm^{-1} in both physical mixtures shifted to 1535 cm^{-1} in inclusion complexes with βCD and 1531 cm^{-1} with HPβCD, respectively.

As discussed above, the nature of carriers played an important role in the formation of inclusion complex prepared by grinding. PRH could form inclusion complex with HPβCD, but yield no inclusion complex with βCD, which might be due to the higher wetting and better complexing ability of HPβCD to PRH.

3.5. Dissolution tests

The dissolution diagrams of PRH and binary systems of PRH–CD in water at 37 °C are shown in Fig. 8. The dissolution time of PRH from inclusion complexes and physical mixtures was analyzed and $t_{100\%}$ values are presented in Table 1 compared to PRH alone.

The dissolution of PRH from the drug alone was incomplete even in 60 min. All the binary systems with both CDs displayed better dissolution properties compared to PRH alone, including two kinds of physical mixtures, being dispersed and completely dissolved within 30 min (βCD) and 16 min (HPβCD), respectively. Increase in the hydrophilicity of drug by CDs may contribute to the enhancement in dissolution of physical mixtures. All products prepared by various methods displayed a high dissolution rate obviously. As shown in Table 1, the dissolution time of PRH from PRH–βCD was 16 min for grinding, 8 min for the ultrasonic method and 12 min for co-precipitation. Among them, the dissolution time of PRH from grinding was the longest, which suggested that PRH and βCD were difficult to react with each other when they both were in solid state.

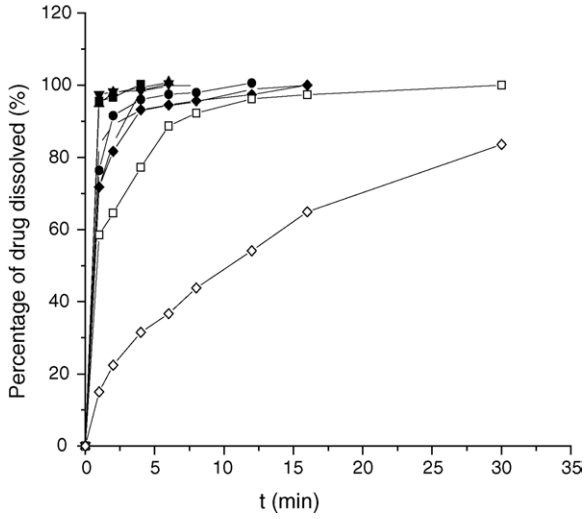

Fig. 8. The dissolution diagram of PRH at 37 °C: (◊) PRH; PRH–βCD system: (□) physical mixture; (☆) inclusion complex by grinding; (★) inclusion complex by ultrasonic method; (●) inclusion complex by co-precipitation; PRH–HPβCD system: (◆) physical mixture; (▼) inclusion complex by grinding; (▲) inclusion complex by ultrasonic method; (■) inclusion complex by co-precipitation.

Table 1
The dissolution time of PRH in water at 37 °C

Sample resources	Dissolution time (min)	
	βCD	HPβCD
PRH	90	90
Physical mixtures	30	16
Grinding	16	6
Ultrasonic method	8	6
Co-precipitation	12	4

The increment in drug dissolution from the PRH–HPβCD systems was higher than from the corresponding ones with the parent CD, showing the importance of the proper choice of the carriers. The better effectiveness of HPβCD was the results of its greater water solubility, higher wetting and complexing ability to PRH, although the phase solubility studies had achieved lower $K_{1:1}$ value, compared with βCD. The dissolution time was 6 min for grinding, 6 min for ultrasonic method and 4 min for co-precipitation, respectively.

4. Conclusion

PRH can form 1:1 molar ratio inclusion complexes with HPβCD by grinding, ultrasonic method and co-precipitation and also with βCD by the later two methods. Enhancement of the solubility of PRH was observed in the presence of CDs under experimental condition, which was 27.6% for βCD and 226.4% for HPβCD. Either ultrasonic method or co-precipitation was better than grinding in respect of dissolution

properties of PRH. The employment of HPβCD could be justified by its superior performance.

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