Preparation and evaluation of inclusion complexes of carvedilol

Saurabh Bhutani, S N Hiremath*, P V Swamy and S A Raju

Department of Pharmaceutical Technology, H K E Society’s College of Pharmacy, Sedam Road, Gulbarga 585 105

Received 26 February 2007; revised 07 May 2007; accepted 05 June 2007

Inclusion behaviour of hydroxypropyl β-cyclodextrin (HPβ-CD) was studied towards carvedilol, an antihypertensive agent, in order to develop a new oral dosage form with enhanced dissolution rate and bioavailability, following cyclodextrin complexation. Formation of inclusion complexes with HPβ-CD in the solid state was confirmed by DSC and FTIR and comparative studies on in-vitro dissolution were carried out. Phase solubility studies indicated formation of 1:1 M complex for HPβ-CD. Apparent stability constant (Kc) was found to be 582.78 M$^{-1}$ for HPβ-CD complexes. DSC studies indicated formation of solid inclusion complexes of carvedilol–HPβ-CD at 1:2 M ratio prepared by kneading method. Solid complexes of carvedilol-HPβ-CD at 1:2 M prepared by physical and kneading method exhibited higher dissolution rate and dissolution efficiency values than the pure drug and other complexes.

Keywords: Carvedilol, Hydroxypropyl β-cyclodextrin, Kneading method, Physical mixture

Introduction

Carvedilol (CRL), an antihypertensive agent, is used in the treatment of hypertension congestive heart failure, cardiac arrhythmias and angina pectoris$^{1,2}$. It is a non-selective β-adrenergic blocker with selective α-adrenergic blocking. However, drug bioavailability is very limited (25-30%), since it is practically insoluble in water and its dissolution is rate limiting for its absorption from the gastrointestinal tract. Cyclodextrins (CDs) form inclusion complexes (ICs) with water insoluble drugs. Natural CDs are cyclic oligosaccharides, containing 6 (α-cyclodextrin), 7 (β-cyclodextrin) or 8(γ-cyclodextrin) α-1,4-linked glucopyranose units, with hydrophilic outer surface and hydrophobic cavity$^{3,4}$. ICs improve stability$^5$, solubility, dissolution rate$^6,7$ and bioavailability$^8$.

This study aims to improve dissolution rate of CRL in aqueous solution through formation of ICs with 2-hydroxypropyl β-cyclodextrin (HPβ-CD), thereby improve its oral bioavailability.

Materials and Methods

Materials

CRL was obtained as a gift sample from Inogent labs, Hyderabad. HPβ-CD was obtained as a gift sample from S A Pharmachem, Mumbai. All other reagents and solvents were of analytical grade and double distilled water was used throughout the study.

Phase Solubility Studies

In phase solubility studies, an excess of CRL was added to 50 ml volumetric flasks containing distilled water (25 ml) with successively increasing quantities (0, 2, 4, 6, 8, 10 and 12 mM) of HPβ-CD$^9$. Flasks were sealed and brought to solubility equilibrium at room temperature after shaking for 72 h. After equilibrium, the content of each flask was filtered through a Millipore membrane (0.45 µm). The filtered solutions were appropriately diluted and the amount of dissolved CRL was determined spectrophotometrically at 242 nm (Shimadzu UV-1700 spectrophotometer). Apparent 1:1 M stability constant (Kc) was calculated from the phase solubility diagram as

\[ Kc = \frac{\text{slope}}{S_0 (1 - \text{slope})} \]

where $S_0$ is solubility of CRL in the absence of CDs.

Preparation of Physical Mixture and Inclusion Complexes (ICs)

Physical mixtures [CRL: HPβ-CD (1:1 and 1:2 M)] were prepared by simple trituration for 1 h in a glass mortar, passed through sieve no.100 and stored in a dessicator.

*Author for correspondence
E-mail: snhiremath@rediffmail.com
For ICs, Stoechiometric quantities of CRL and HPβ-CD (1:1 and 1:2 M) were triturated with a small amount of 50% ethanol. Slurry was kneaded for 1 h and dried at 25°C for 24 h, pulverized and passed through sieves no.100 and stored in a dessicator.

Characterization of Prepared Complexes

**IR-Spectroscopy**

IR spectra of CRL and their complexes were determined by KBR pellet method by Perkin Elmer FT-IR series model-1615 spectrophotometer.

**Differential Scanning Calorimetry (DSC)**

DSC was carried out using aluminium sample pans at scanning speed of 10°C per min from 50°C to 600°C.

In-vitro Dissolution Studies

**In vitro** dissolution of CRL ICs was studied in USP XXIII dissolution apparatus (Electrolab) employing a paddle stirrer. Dissolution medium contained 0.1 N HCl (900 ml) at 37±0.5°C, which was maintained throughout the experiment. Complex equivalent to 12.5 mg of CRL was used in each test. Samples (5 ml each) of dissolution medium were withdrawn by syringe fitted with pre-filter at known intervals and analyzed for drug release by measuring absorbance at 241.2 nm after suitable dilution with 0.1 N HCl. The volume withdrawn at each interval was replaced with fresh quantity of dissolution medium.

Results and Discussion

**Phase Solubility Studies**

Phase solubility diagram for complex formation between CRL and CD in water is A_L type for HP β-CD, (Fig. 1), which illustrate solubility enhancement capability of CD. Aqueous solubility of CRL increased linearly (r=0.994) as a function of HP β-CD concentration with K_c of 582.78 M⁻¹.

**FT-IR Studies**

FT-IR studies indicated weak interaction of CRL with HP β-CD at 1:2 M prepared by kneading method (Fig. 2). In CRL spectra, absorption peaks were observed at 3344.94 cm⁻¹ and 2923.24 cm⁻¹ due to hydroxyl and amine stretching respectively. Peak at 1215.74 cm⁻¹ and 1032.14 cm⁻¹ are due to alkyl aryl ether stretching and bending vibrations respectively.

In the formulation P1 containing drug, HP β-CD at 1:1 M ratio prepared by physical mixture exhibited a peak due to alkyl aryl ether stretching at 1217.06 and 1032.32 indicating weak interaction between drug and HP β-CD.
Fig. 3 — DSC thermograms of pure carvedilol (5), HPβ-CD (1) and formulations [P(6), P(2), K(3) and K(4)].
In case of formulation P₂ containing drug, HPβ-CD at 1:2 M ratio prepared by physical mixture (P₂), peak due to alkyl aryl ether stretching was obtained at 1215.74 and 1032.14 indicating no interaction between drug and HPβ-CD. But in the formulation K₁ containing drug, HPβ-CD at 1:1 M ratio prepared by kneading method, peak due to alkyl aryl ether stretching was obtained at 1215.47 and 1033.22 indicating weak interaction between drug and HPβ-CD. Also in the formulation K₂ containing drug, HPβ-CD at 1:2 M ratio prepared by kneading method (K₂), peak due to alkyl aryl ether stretching was obtained at 1214.60 and 1031.99 indicating weak interaction between drug and HPβ-CD.

**DSC Studies**

Thermal behaviour of CD ICs was studied using DSC in order to confirm the formation of solid ICs. When guest molecules are incorporated in CD cavity or in crystal lattice, their melting, boiling and sublimation points usually shifted to a different temperature or disappear within the temperature range, where CD lattice is decomposed. DSC thermogram of CRL showed an endothermic peak at 123.00°C corresponding to its melting point (Fig. 3). Thermogram of HPβ-CD showed a very broad endothermic effect, which attained a maximum around 100°C due to release of water molecules and peak at 328°C corresponding to its melting point.

Thermograms of CRL and HP-β-CD (1:1 M) prepared by physical (P₁) and kneading (K₁) method showed broadened endothermic peak at 95-105°C. This may be due to shift of characteristic peak of CRL, which was observed at 123°C, indicates weak interaction of drug and HP-β-CD.

Thermal curve of CRL-HPβ-CD, prepared by physical (P₂) and kneading (K₂) method (1:2 M), has shown a peak at 75°C due to dehydration process of HPβ-CD. Complete disappearance of endothermic peak due to CRL with these systems indicated the formation of an amorphous solid dispersion of the molecular encapsulation of drug that involves CD cavity, or both in case of complexes prepared with CRL: HPβ-CD at 1:2 M ratio.

**In vitro Dissolution Studies**

All the complexes exhibit a faster dissolution rate than pure CRL (Fig. 4). The release of CRL from ICs prepared at 1:2 M ratio was found to be fast, releasing entire drug in 2 min when compared to ICs prepared at 1:1M ratio (4 min) and pure drug which showed approx 90% of drug release in 120 min. Increase in dissolution rate of CRL is 10.45 fold when under the form of IC, obtained from HPβ-CD by kneading method (Table 1). A marked improvement in dissolution rate of CRL was observed with K₂ prepared by kneading method. Improved dissolution in case of kneading method with HPβ-CD may be due to the formation of solid IC with better interaction of drug and CD during kneading process.

**Conclusions**

HPβ-CD can be used to prepare CRL ICs. Solubility of CRL in 0.1 N HCl was improved greatly as a result of complex formation with HPβ-CD in comparison to pure CRL. A marked increase in the dissolution of IC was observed with HPβ-CD at 1:2 M prepared by kneading method. CRL-CD complexation results in an increase of solubility and dissolution rate for the drug suggesting a possible enhancement of its oral bioavailability.

**Acknowledgements**

Authors thank M/s S A Pharmachem and Pharma trade, Mumbai, for providing polymer and drug samples,
References


