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ORIGINAL ARTICLE

Preparation and characterization of inclusion complexes of carvedilol with methyl-β-cyclodextrin

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Abstract Aim of the present work was to investigate the effect of methyl-β-cyclodextrin (MβCD) on the solubility and dissolution rate of carvedilol (CAR), a drug used orally for the treatment of hypertension. Phase solubility studies showed an A_L-type diagram indicating the formation of inclusion complex in 1:1 molar ratio. Solid binary systems of the drug with MβCD were prepared by various methods. Physicochemical characterizations were performed using Fourier Transformation Infrared Spectroscopy, Differential Scanning Calorimetry and powder X-Ray Diffractometry. It could be concluded that CAR can form inclusion complex with MβCD. The dissolution profiles of inclusion complexes were determined and compared with those of CAR alone and the physical mixture. The dissolution rate of CAR was increased by MβCD inclusion complexation remarkably.

Keywords Carvedilol · Methyl-β-cyclodextrin · Phase solubility studies · Characterization · Dissolution

Introduction

It is well known that many drugs show bioavailability problems due to their low water solubility and slow dissolution rate. Complexation with cyclodextrins has been widely used to improve the solubility and dissolution rate of poorly soluble drugs [1–3]. Cyclodextrins (CDs) are macrocyclic oligosaccharides with six to eight D-glucose units called α-cyclodextrin, β-cyclodextrin and γ-cyclodextrin. The most important structural feature of CDs is that they have hydrophobic central cavities capable of forming stable complexes with properly sized drug molecules [4–6].

β-Cyclodextrin (βCD) is easily accessible, low priced but less soluble in water, due to hydrogen bonding network between hydroxyl groups of CDs and water molecules [7]. Methylation prevents formation of hydrogen bonds and improves solubility and this generally results in more extensive solubilisation ability towards lipophilic molecules [8]. Hence methyl-β-cyclodextrin (MβCD) was selected for complexation. MβCD is readily soluble in water and less hygroscopic. Methylation on the hydroxyl units favorably extends the hydrophobic cavity without any steric hindrance and provides greater inclusion ability. The methylated βCD markedly improve the solubility, rate of dissolution and absorbability from different sites in the body for poorly water soluble drugs [9].

Carvedilol (CAR), a nonselective β-adrenergic blocking agent, is used in the treatment of hypertension, angina pectoris and congestive heart failure [10]. However its poor aqueous solubility is one of the reasons for its limited bioavailability after oral administration [11].

The objective of present work was to investigate the possibility of complex formation of CAR with MβCD. The inclusion complexes were prepared by co-grinding, kneading and co-evaporation methods. Stability constant of the complexation was established according to phase solubility studies. The dissolution properties of inclusion complexes were evaluated and compared with those of CAR alone and the corresponding physical mixtures. Fourier Transformation Infrared Spectroscopy (FTIR), Differential Scanning Calorimetry (DSC) and X-Ray Diffraction (XRD) were used to characterize the solid states of the binary systems.

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Materials and methods

Materials

CAR was kindly supplied by Sun Pharmaceuticals, India. MβCD (D.S. = 1.8 and M.W. = 1310) was gifted by Wacker fine chemicals. These chemicals were used as received without further purification. All other reagents were of analytical reagent grade purity. Double distilled water was used throughout the study.

Phase solubility studies

Phase solubility studies were carried out as per the method described by Higuchi and Connors [12]. An excess amount of CAR (20 mg) was added to 5 mL of water or MβCD aqueous solution (0–10 mM) in sealed glass containers. The suspensions were shaken at room temperature for 48 h. After equilibrium attainment, the samples were filtered and properly diluted. The concentration of CAR was determined spectrophotometrically using UV visible spectrophotometer—Shimadzu (Model UV-1601) at 285 nm. The apparent stability constant Ks was calculated from the phase solubility diagram according to the following equation:

$$K_s = \frac{\text{Slope}}{s_0(1 - \text{Slope})}$$

S_0 is the solubility of CAR in absence of MβCD.

Preparation of binary systems of CAR-MβCD

The binary systems of CAR-MβCD with 1:1 molar ratio were prepared by various methods such as co-grinding (CG), kneading (KN) and co-evaporation (CE). The physical mixture (PM) was also prepared for the purpose of comparison. CG product was obtained by co-grinding CAR and MβCD with intense trituration for 30 min in glass mortar. KN product was obtained by triturating CAR and MβCD in glass mortar for 20 min, then kneading with 66% alcohol for 45 min. The pasty mass obtained was dried at 60 °C. The dried mass was passed through sieve no. 80 and stored overnight in desiccator. For preparation of CE product, equimolar amounts of MβCD and CAR were dissolved in minimum volume of 1:1 mixture of 66% ethanol and water. The final solution was stirred with the help of magnetic stirrer at 60 °C till pasty mass was obtained. The pasty mass was treated as above to get the dry sample.

Analysis of drug content in binary mixture

Samples of each binary mixture were assayed for drug content by dissolving 5 mg equivalent in 50 mL of methanol with subsequent suitable dilution. The drug content was determined spectrophotometrically at 285 nm.

Differential scanning calorimetry

DSC measurements were carried out using a Mettler Toledo DSC 822. Samples of drug, MβCD and binary mixtures containing drug were placed in sealed aluminum pans and heated at 10 °C/min in the range of 30–200 °C, using an empty sealed pan as a reference. (Dry nitrogen was used as purge gas.)

Fourier transformation infrared spectroscopy

Infra-Red spectra were obtained using Jasco-700 FTIR Spectrophotometer using KBr discs. The instrument was operated under dry air purge and the scans were collected at scanning speed of 2 mm/sec with resolution of 4 cm^{-1} over the region of 4,000–400 cm^{-1}.

X-Ray diffractometry

Powder X-ray diffraction patterns were recorded using Ni-filtered CuKα radiation, a voltage of 40 Kv and a current of 30 mA. The scanning rate employed was 1 °C/min and samples were analyzed between 2θ angles of over 5–45°. The powder diffraction patterns of CAR, MβCD, PM and inclusion complexes were recorded.

Dissolution studies

The dissolution rate studies of CAR alone and from various CAR-MβCD systems were conducted using USP XXIII dissolution apparatus type-II (6 stations, VDA-6DR, Veego Scientific, India) at 37 ± 0.5 °C stirring at 50 rpm. Ten mg of CAR or its equivalent amount of CAR-MβCD binary system was added to 1,000 mL of phosphate buffer pH 6.8. The samples were withdrawn at predetermined time intervals and analyzed spectrophotometrically at 285 nm.

Results and discussion

Phase solubility studies

The phase solubility profile of CAR-MβCD is presented in Fig. 1. According to Higuchi and Connors the phase solubility diagram of CAR-MβCD could be classified as A_L type. The curve showed a linear increase in CAR solubility as a function of MβCD concentration with a slope of 0.0104 ($R^2 = 0.9913$) in the concentration range (0–10 mM) investigated. The apparent stability constant $K_{1:1}$ was 277 M^{-1} as compared to 50 M^{-1} for hydroxypropyl-

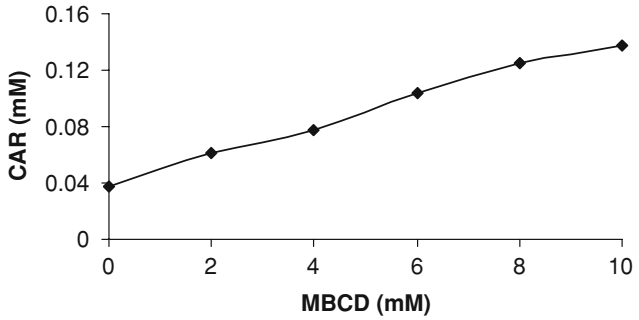

Fig. 1 Phase solubility profile of CAR-MβCD in water

Table 1 Drug content in the binary mixtures

System	% Drug content (±SD)
Physical mixture	99.77 ± 0.427
Co-ground product	99.7 ± 0.364
Co-evaporated product	100.24 ± 0.483
Kneaded product	99.81 ± 0.408

β-cyclodextrin (HPβCD) [13]. Slope value was lower than one indicating that inclusion complex in the molar ratio of 1:1 between the guest (CAR) and the host (MβCD) molecule was obtained.

Analysis of drug content in binary mixture

Actual drug content in each binary mixture was determined. The results are reported in Table 1. As can be seen, PM, CG, CE and KN products showed a good agreement between theoretical and actual drug content.

Differential scanning calorimetry

DSC can be used for the recognition of inclusion complexes. When the guest molecules were embedded in the CD cavity, their melting, boiling or sublimation points generally shifted to a different temperature [13]. The thermograms of CAR and the binary systems are shown in Fig. 2. The thermogram of CAR was typical of a highly crystalline compound, characterized by a sharp endothermic peak at 118 °C which corresponded to its melting [14]. The DSC thermogram of MβCD showed a broad endotherm in the range of 100–120 °C, which could be attributed to the release of water molecule from the cavity (desolvation). A similar observation was made by Mura in the case of βCD [15]. The endothermic peaks of drug and MβCD were retained in PM showing no interaction between them. In case of CG and CE systems the endothermic peak of drug was shifted to lower temperature indicating some type of interaction between drug and

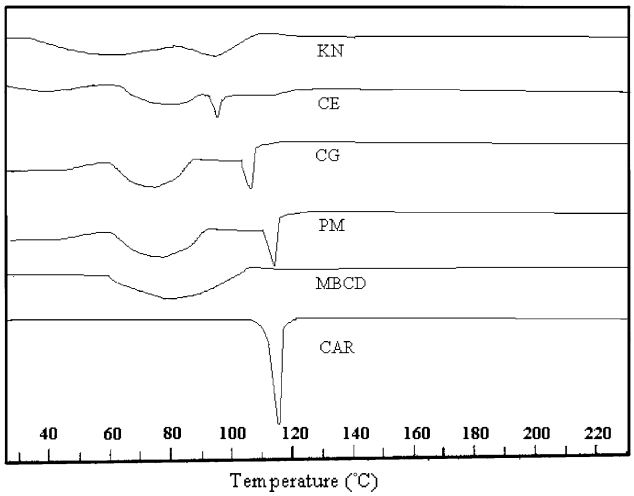

Fig. 2 DSC thermograms of CAR-MβCD systems: Carvedilol (CAR), Methyl-β-cyclodextrin (MβCD), physical mixture (PM), co-ground (CG), co-evaporated (CE) and kneaded (KN) systems

MβCD [16]. In these systems, their may be occurrence of reduction in drug crystallinity or probably a partial dispersion at a molecular level in the solid product [17]. In the case of KN systems a shallow, less intense endotherm was obtained at 98 °C suggesting complex formation. These results were in good agreement with those previously reported by Miro et al for CAR-HPβCD complex [13]. The DSC thermogram of prazosin hydrochloride-HPβCD complex showed disappearance of endothermic peak of drug but presentation of a new peak with reduced intensities as a consequence of interaction between the components [4].

Fourier transformation infrared spectroscopy

CAR, (±)-1-(Carbazol-4-yloxy)-3-[[2-(o-methoxyphenoxy)ethyl] amino]-2-propanol is a racemic mixture with the structure as shown in Fig. 3. Infrared spectra of CAR, MβCD as well as those of the binary systems are presented in Fig. 4. CAR alone showed characteristic bands belonging to carbazol moiety at 1,253, 1,502 and 2,922 cm^{-1} corresponding to aromatic secondary C–N vibrations, C–C multiple bond stretching and C–H stretching of aromatic ring respectively, which remained unchanged in the physical mixture. All the binary mixtures of CAR-MβCD did not show any new peaks indicating that no chemical bonds were created in the formed complexes. Disappearance of the above characteristic peaks in the CG, KN and CE products, suggested entrapment of the carbazol moiety into the host cavity during inclusion complexation. Koester et al in the study of complexation of Carbamazepine with βCD found that the drug characteristic peaks were retained in the physical mixture as contrast to complex [18].

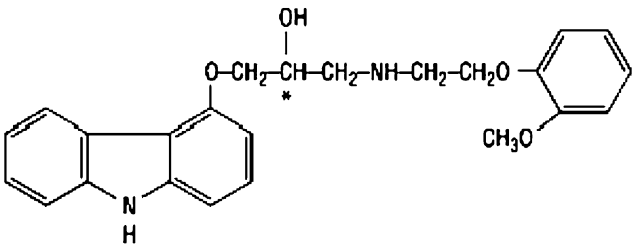

Fig. 3 Chemical structure of CAR

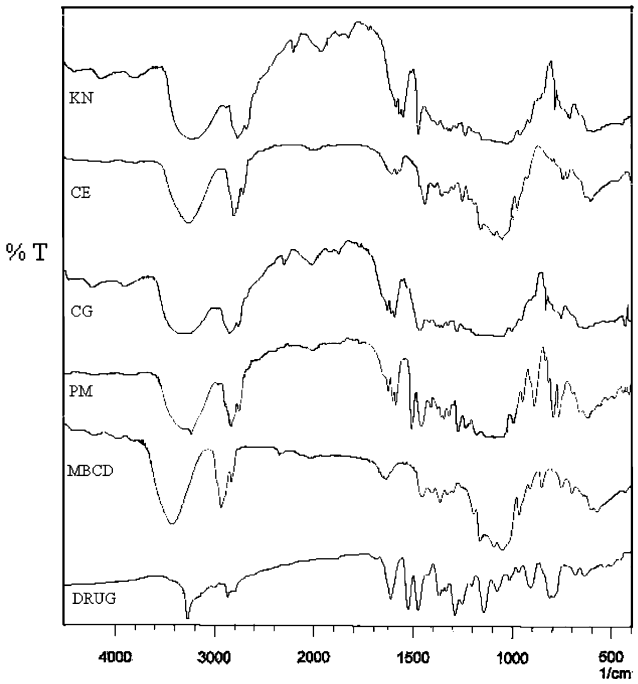

Fig. 4 FTIR spectra of CAR-MβCD systems: Carvedilol (CAR), Methyl-β-cyclodextrin (MβCD), physical mixture (PM), co-ground (CG), co-evaporated (CE) and kneaded (KN) systems

X-Ray diffraction

The XRD patterns of CAR, PM and KN complex are illustrated in Fig. 5. Significantly different XRD patterns are to be expected if an inclusion complex is formed, because crystal structure will be changed [19]. It was seen that the diffraction pattern of the physical mixture was simply superimposition or summation of the drug and MβCD with similar sharp peaks and much similar d (interplanar distance) values. Nevertheless some changes like peak locations, reduction in peak intensities and small differences in the d values were observed in the diffractograms of the PM (Table 2) indicating the possibility of some types of interaction between MβCD and CAR. The CG and CE systems presented a diffraction patterns quite similar to that of physical mixture but with lower intensity and overlapping between some CAR and MβCD peaks. Diffraction pattern of KN sample showed two very broad bands of much reduced

Table 2 Peak intensities of CAR in XRD patterns of CAR-MβCD binary systems

2θ	CAR	MβCD	CAR: MβCD			
			PM	CG	CE	KN
6.05	2282	–	243	89.74	125	–
15.05	2943	–	450	249.37	453	–
17.55	2767	–	179	346	411	–
17.76	3726	–	504	426	553	–
18.63	3724	–	723	713	918	–
24.464	3803	–	596	521	776	–
26.59	1903	–	510	444	595	–
12.53	–	819.7	230	–	–	207
18.63	–	866.72	723	713	918	277

intensities with disappearance of the diffraction peaks of the drug. Zingone et al found similar results for Warfarin-βCD complexes [20]. In the case of Nifedipine-βCD kneaded syetem, the XRD pattern appeared to be different regarding the superposition of the Nifedipine and βCD patterns [21]. These phenomena confirmed that an inclusion complex between drug and MβCD was formed.

Dissolution studies

The dissolution rate profiles of CAR and its binary systems are reported in Fig. 6. Dissolution of CAR was incomplete even after three h. Release rate from the inclusion complexes prepared by various methods were evidently higher than the dissolution rate of drug alone. Corresponding physical mixture, also demonstrated higher dissolution profile which may be due to an improved wettability of the drug particles at the early stages of dissolution process [22]. All the products prepared by various methods displayed a high dissolution rate. Amongst them dissolution rate of CAR from CG system was less which suggested that CAR and MβCD were difficult to react with each other when they were in solid state. The KN product gave complete release at the end of 60 min. A very high increase of the drug dissolution rate in case KN system may be probably due to several reasons: the formation of soluble inclusion complex, amorphization of the drug and consequent solubility increase, better wettability and reduction of particle size [23]. Improvement in the dissolution rate of Triamterene [24], Camptothecin. [25], Furnidipine [26] and Celecoxib [27] has been observed after CD complexation.

Conclusions

Results of the characterization studies indicated the promising formation of new solid phases allowing to the

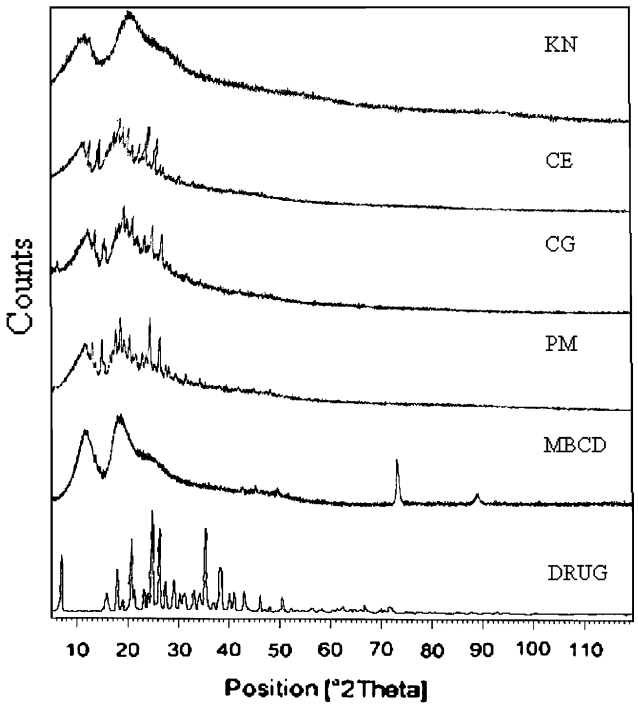

Fig. 5 X-Ray diffractograms of CAR-MβCD systems: Carvedilol (CAR), Methyl-β-cyclodextrin (MβCD), physical mixture (PM), Co-ground (CG), co-evaporated (CE) and kneaded (KN) systems

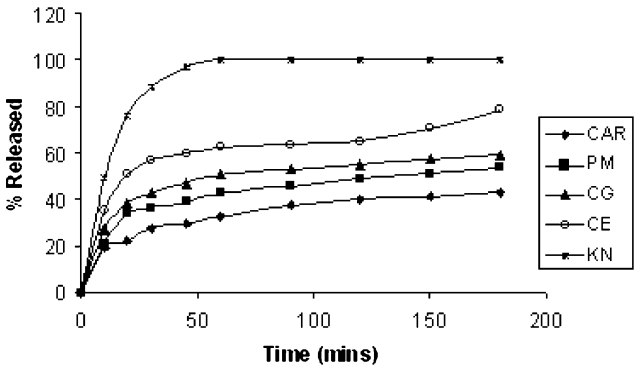

Fig. 6 The dissolution diagram of CAR-MβCD systems: —◆— Carvedilol (CAR), —■— physical mixture (PM), —▲— co-ground (CG), —○— co-evaporated (CE) and —✱—kneaded (KN) systems

conclusion of strong evidences of binary inclusion complex formation between CAR and MβCD. The complexes exhibited improvement in solubility and dissolution rate of drug. Studies are under process to evaluate the possible enhancement in the bioavailability from these systems after incorporation into suitable dosage form.

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