



Drug Complexation and Formulation of a Buccal Tablet

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Abstract

In the present work use of Beta-Cyclodextrin for inclusion of Carvedilol, an antihypertensive drug with poor solubility and high first pass metabolism was studied, in order to improve its dissolution rate. The complex prepared by kneading method was characterized by Differential Scanning Calorimetry, Fourier Transformation Infra Red Spectroscopy and X-Ray Diffractometry along with the plain drug and physical mixture. The drug so complexed was incorporated into a buccal dosage form to by pass first pass metabolism to improve its bioavailability. The buccal tablets containing complex showed reasonable mucoadhesive strength. The dissolution and permeability across pig buccal mucosa were improved in case of tablets containing the complex as compared to plain drug tablet.

Key words: Carvedilol, Beta-Cyclodextrin, Complexation, Dissolution, Characterization, Permeation.

Introduction

Carvedilol (CAR) is a non selective β adrenergic antagonist widely used to treat hypertension and angina pectoris (Moser and Frishman 1998). It is sparingly soluble in water (Dunn *et al.* 1997) and shows high first pass metabolism (Mollendroff and Neugebauer 1987). The low drug bioavailability is attributed to these two factors. The first part of the present work aims at improving the water solubility of the drug by forming the inclusion complex with Beta Cyclodextrin (β -CD). CDs are water soluble cyclic oligosaccharides with a cone shaped structure. Due to their particular conformation they are able to include a guest molecule inside their hydrophobic cavity forming a noncovalently bonded complex, resulting in its improved solubility. Solubility of various drugs has been improved by CD complexation (Miyake *et al.* 1999; Longxiao and Suyan. 2006; Perdomo- Lopez *et al.* 2002; Badawy *et al.* 1996; Ammar *et al.* 2006). Buccal route has been successfully utilized for administration of drugs undergoing high first pass metabolism and degradation in the harsh gastrointestinal environment (Miyazaki *et al.* 1995). Buccal drug absorption can be promptly terminated in case of toxicity by removing the dosage form from the buccal cavity. CAR exhibits high first pass metabolism of 80 % (Mollendroff and Neugebauer 1987). Hence its bioavailability can be increased by administration by buccal route. The second part of the present work involves formulation of a buccal tablet incorporating the CAR- β CD complex.

Materials and Methods

CAR was kindly supplied by Sun Pharmaceuticals, India. β CD (M. W. = 1135) was gifted by Signet chemical Corporation. Carbopol 974 P was received as a gift sample from Noveon. 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.

Preparation and characterization of CAR- β CD binary systems

For preparation of binary systems, CAR and β CD were used in 1:1 stoichiometric ratio. Physical mixtures were prepared by mixing the drug and β CD and passing through 100# sieve. For the kneaded product, the mixture was triturated for 15 min in a mortar followed by addition of minimum amount of 66% alcohol. The mixture was ground thoroughly for 45 min to obtain paste which was dried at 60° C overnight. The resultant powder was ground, passed through 100# sieve and stored in a dessicator. CAR- β CD binary systems were characterized by Differential Scanning Calorimetry (DSC) on a Mettler Toledo DSC 822. Samples of drug, β CD 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

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purge gas. The powder X-ray diffraction patterns of CAR, β CD, PM and inclusion complex were recorded using Phillips P Analytical X'Pert PRO powder X-Ray diffractometer (Netherlands) using Ni-filtered, $\text{CuK}\alpha$ radiation, a voltage of 40 kV and a current of 30 mA. The scanning rate employed was 1° per min and samples were analyzed between 2 angles of over $5\text{-}45^\circ$. 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 $4000\text{-}400\text{ cm}^{-1}$.

Preparation of buccal tablets

For preparation of buccal tablets, CAR binary system equivalent to 6.25 mg of CAR, 63.24 mg of lactose DCL, 7.5 mg of carbopol 974 P, 15 mg sodium carboxy methyl cellulose, 1mg of magnesium stearate and 2 mg of talc previously screened through 100# sieve were mixed and compressed on a single punch machine using 9 mm circular flat beveled punch. The backing membrane of ethyl cellulose was compressed over it in order to get unidirectional release of the drug. For comparison purpose tablets containing only CAR were also prepared.

In vitro dissolution studies

Dissolution of CAR from the CAR- β CD complex and buccal tablets containing CAR- β CD complex equivalent to 10 mg and 6.25 mg of CAR respectively were evaluated in buffer pH 6.8 using USP XXIII dissolution apparatus type-II (6 stations, VDA-6DR, Veego Scientific, India) at $37 \pm 0.5^\circ\text{C}$ stirring at 50 rpm. For tablets 900 ml and for complex 1000 ml of dissolution medium was used. The samples were withdrawn at predetermined time intervals and analyzed spectrophotometrically at 285 nm.

Porcine buccal mucosa preparation

Porcine buccal tissue from domestic pigs was obtained from local slaughterhouse. The mucosal membrane was excised by removing connective and adipose tissue and was equilibrated at $37 \pm 0.1^\circ\text{C}$ for 30 min in phosphate buffer pH 7.4.

Ex Vivo drug permeation studies

The buccal epithelium was carefully mounted in between the two compartments of Modified Franz Diffusion cell. Buccal tablets containing plain drug and complexed drug were tested. The tablets were stuck to the mucosa in the donor side.

Receiver medium was a mixture of alcohol, propylene glycol, phosphate buffer pH (7.4) in a ratio of 40:15:45 maintained at $37\pm 0.1^\circ\text{C}$ under gentle stirring. From the receiver compartment, 2 ml aliquot was collected at predetermined time intervals and replaced by an equal volume of alcohol, propylene glycol, phosphate buffer solution. Analysis of samples was performed using a Jasco 2000 HPLC system equipped with a pump-PU 2080, UV / Vis detector (Jasco UV 2075) and a reverse phase column HIQSIL C18 (250 X 4.6 mm, $5\ \mu\text{m}$) at ambient temperature. The mobile phase was a mixture acetonitrile and phosphate buffer (0.05M KH_2PO_4 at pH 4.5) (60:40, v/v) run at 0.8 ml/min.

Measurement of mucoadhesive force

The mucoadhesive force was checked by using Modified Balance Test (Gupta *et al.* 1992). Porcine buccal mucosa was tied with its mucosal side out onto the lower teflon cylinder. The tablet was stuck to the upper teflon cylinder using cyanoacrylate adhesive and lowered onto the mucosa under constant weight of 5 g for a total contact time of 1 min. Mucoadhesive strength was assessed in terms of weight required to detach the tablet from the membrane.

Results and Discussion

The DSC profiles of pure components (CAR and β CD) and binary systems in melting range of the drug and carriers dehydration are shown in Fig. 1. 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 (Miro *et al.* 2006). The DSC thermogram of β CD showed a broad endothermic effect around in the range of $100\text{-}120^\circ\text{C}$, associated to crystal water loss from β CD (Hassan *et al.* 1990). The endothermic peaks of drug and β CD were retained in PM showing no interaction between them. In case of KN systems the endothermic peak of drug disappeared and new one appeared at 93°C , similar to observation made for haloperidol (Loukas *et al.* 1997). The XRD pattern for CAR (Fig. 2) indicated characteristic peaks which were retained in the case of PM. However, the XRD pattern of KN sample was devoid of crystalline drug peaks which were similar to observation made in the case of budesonide-HP β CD complex (Bandi *et al.* 2004). FTIR spectrum of CAR (Fig. 3) indicated aromatic secondary C-N vibrations at 1253, C-C multiple bond stretching at 1502 and C-H stretching of aromatic ring at 2922 cm^{-1} which remained

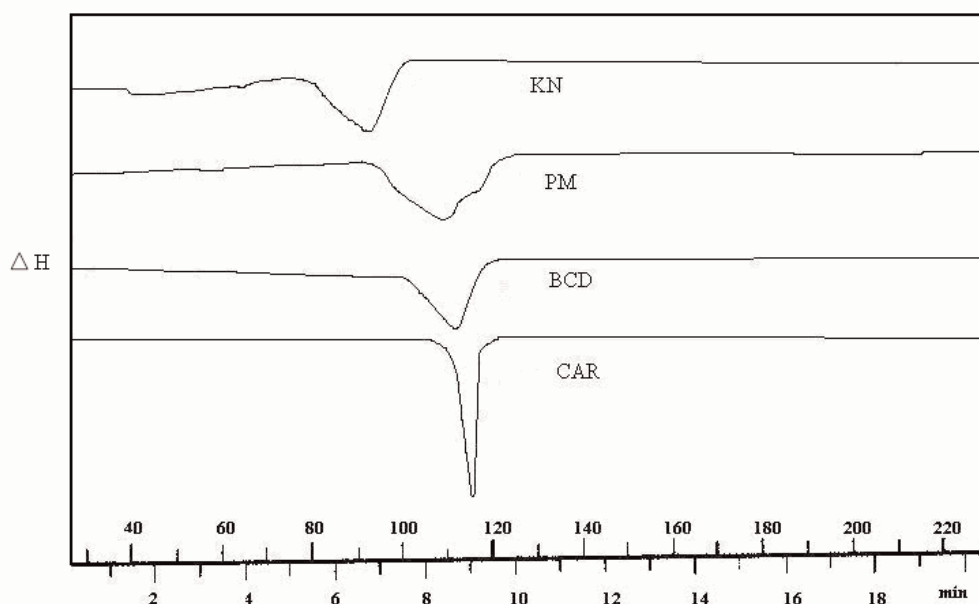


Fig. 1. DSC Thermograms of CAR- β CD system: Carvedilol (CAR), β -cyclodextrin (BCD), Physical mixture (PM) and Kneaded (KN) system

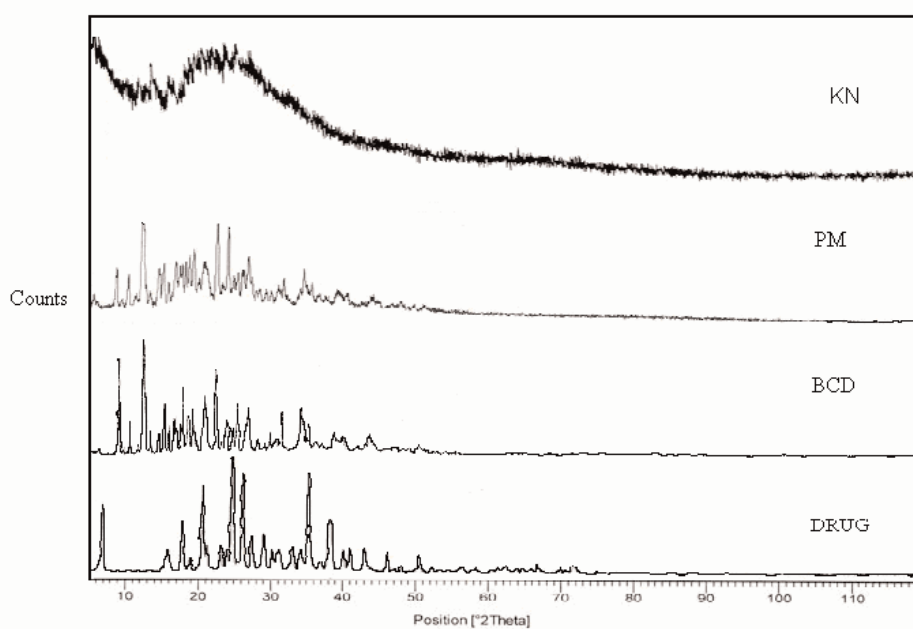


Fig. 2. X-Ray Diffractograms of CAR- β CD system: Carvedilol (CAR), β -cyclodextrin (BCD), Physical mixture (PM) and Kneaded (KN) system

unchanged in the physical mixture. CAR- β CD KN sample showed disappearance of the above characteristic peaks, suggesting possibility of entrapment of CAR into the host cavity during inclusion complexation.

The dissolution rate profiles of CAR and its binary systems are reported in Fig. 4. Dissolution of CAR was incomplete even after 3 hrs. The KN product gave complete release at the end of 120 mins. Improvement in dissolution rate of

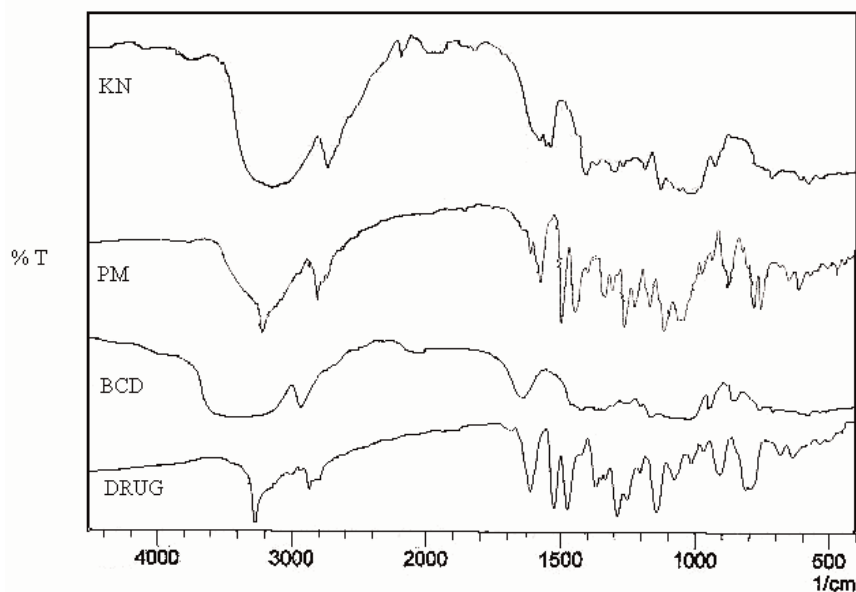


Fig. 3. FTIR spectra of CAR- β CD system: Carvedilol (CAR), β -cyclodextrin (BCD), Physical mixture (PM) and Kneaded (KN) system

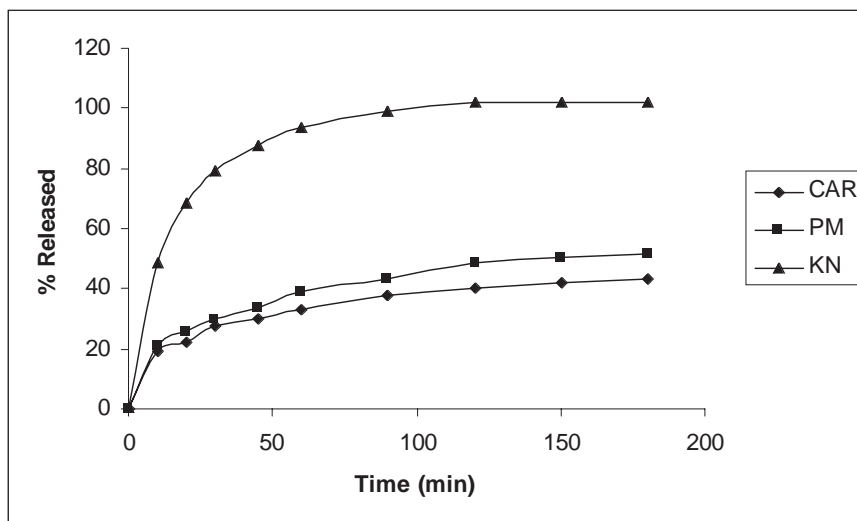


Fig. 4. Dissolution profile of CAR- β CD system in phosphate buffer pH 6.8. Carvedilol (CAR), Physical mixture (PM) and Kneaded (KN) system

Meloxicam (Abdoh *et al.* 2007), Imatinib (Beni *et al.* 2007), Bupivacaine (Morales *et al.* 2007) and Sildenafil (Al Omari *et al.* 2006) has been reported after complexation with cyclodextrins. Results of *in vitro* dissolution studies of tablets are shown in Fig 5. Complete release of CAR was obtained from tablets containing complexed drug as compared to 41.22 % from tablets containing plain drug at the end of 3.5 hrs. There have been controversial reports regard

ing the effect of β CD on dissolution of drug from tablet formulations. It has been demonstrated that dissolution rate of Diltiazem from the tablets was decreased by addition of β CD (Horiuchi *et al.* 1990). Increased dissolution by inclusion complexation with β CD has been observed for Nifedipine (Chowdary and Kamalakara 2003). Enhanced dissolution by β CD tends to be observed with water insoluble drugs, presumably since dissolution of water insoluble drugs in the

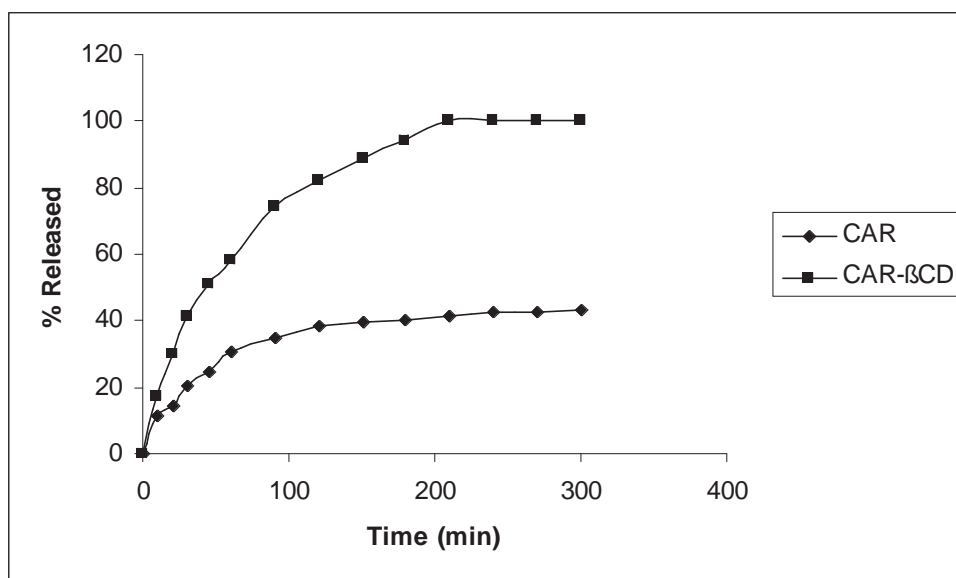


Fig. 5. Dissolution profile of CAR tablets in phosphate buffer pH 6.8. Carvedilol (CAR), Kneaded (KN) system

crystal form would be slower than that for inclusion complexes. CAR being poorly soluble drug, its dissolution from tablets containing complex was improved as compared to the one containing plain drug.

Amount of drug permeated across the porcine buccal mucosa was 5.7 mg and 2.51 mg from tablets containing complexed drug and plain drug respectively. The results stressed the effectiveness of β CD in improving the permeability of CAR across the mucous membrane. It has been reported that permeation of CAR was improved in the case tablets containing CAR-HP β CD complex as compared to plain drug (Cappello *et al.* 2006). Usefulness of CP as buccal mucoadhesive polymer has been reported (Nafee *et al.* 2004). Hence CP 974P was selected in the present formulation. Both the buccoadhesive tablets containing complexed drug and plain drug showed satisfactory mucoadhesive strength of 10 g.

Conclusion

Results of characterization studies indicated that CAR could form inclusion complex with β -CD and improved its dissolution rate. The buccal tablets containing CAR- β CD complex showed better drug dissolution and permeability across buccal mucosa as compared to those containing plain drug. The tables had satisfactory mucoadhesive strength. Thus β -CD can be used satisfactorily to improve dissolution of CAR and use of buccal tablets can possibly improve the bioavailability of CAR by avoiding FPM.

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