

Research Article**DESIGN OF BUCCAL DRUG DELIVERY SYSTEM FOR A POORLY SOLUBLE DRUG**

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ABSTRACT

Carvedilol is an antihypertensive drug used in the treatment of congestive heart failure, cardiac arrhythmias and angina pectoris. It exhibits poor bioavailability of 25-30% which is attributed to its poor solubility and high first pass metabolism. The present work was aimed at overcoming these two limitations. Drug-Methyl- β -cyclodextrin complex was prepared by kneading method and characterized by Fourier Transformation Infrared spectroscopy, Differential Scanning Calorimetry and powder X-Ray Diffractometry studies. Dissolution rate of complex was compared with plain drug and physical mixture. The complex was incorporated into buccal tablet. The buccal tablets were evaluated for drug release, mucoadhesive strength and ex-vivo permeability. Characterization of binary system revealed the formation of inclusion complex of drug with Methyl- β -cyclodextrin. The complex showed complete release as compared to 32.8% and 42.7% from plain drug and physical mixture respectively in 60min. Tablets containing complex showed complete release at the end of 180min compared to 40.23% from tablets containing plain drug. The buccal tablets containing complex had good mucoadhesive strength. The amount of drug permeated from these tablets across the porcine buccal mucosa at the end of 5h was 6.2mg as compared to 2.51mg from tablets containing plain drug. Thus it can be concluded that buccal tablet containing complexed CAR would have improvement in bioavailability.

KEY WORDS: Carvedilol, Methyl-B-Cyclodextrin, Complexation, Dissolution.**INTRODUCTION**

Buccal drug delivery offers distinct advantages over per oral administration for systemic effect. These advantages include possible bypass of first pass effect and avoidance of presystemic elimination within the gastrointestinal tract. Therefore for the drugs having poor bioavailability because of high first pass metabolism, buccal route is preferred. Miyazaki *et al.* prepared oral mucoadhesive tablets of Diltiazem by directly compressing the drug with a mixture of chitosan and sodium alginate which had bioavailability of 69.6% as compared to 30.4% by oral administration¹. Other examples include Diclofenac Sodium², Chlorpheniramine maleate³, Metoprolol tartrate⁴ and Propranolol hydrochloride⁵, all of which had good aqueous solubility. The driving force for transport across buccal mucosa is the concentration gradient which depends upon concentration of drug in saliva. Thus in order for the drug to get absorbed across buccal mucosa, it is necessary that it should be present in solution form. In

case of poorly soluble drugs, solubility can be improved by various approaches. Cyclodextrin complexation process has been emerged as effective tool to increase solubility of poorly soluble drugs. Compared to native β -cyclodextrin, its methylated derivative being more water soluble is preferably used for complexation. Buccal formulation containing cyclodextrin solubilized drug will have dual advantage of increased solubility and avoidance of first pass metabolism.

Carvedilol (CAR), an antihypertensive agent used in the treatment of congestive heart failure, cardiac arrhythmias and angina pectoris, suffers from low bioavailability of 25-30%. Two main reasons for low bioavailability being its poor aqueous solubility⁶ and high first pass metabolism⁷. The present study aims to improve dissolution rate of CAR through complexation with Methyl- β -cyclodextrin (M β CD) and to prepare buccal tablets incorporating the inclusion complex to possibly improve the bioavailability.

MATERIALS AND METHODS

Materials

CAR was kindly supplied by Sun Pharmaceuticals, India. M β CD (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.

Preparation of Solid Binary Systems

The binary system of CAR-M β CD with 1:1 molar ratio was prepared by triturating CAR and M β CD in glass mortar for 20 min, then kneading with 66% alcohol for 45 min. The pasty mass obtained was dried at 60°C. The dry mass was passed through a sieve size of 150 μ m (mesh 100) and stored overnight in desiccator. The physical mixture of CAR and M β CD was also prepared for the purpose of comparison.

Differential Scanning Calorimetry (DSC)

DSC measurements were carried out using a Mettler Toledo DSC 822. Samples of drug, M β CD and binary mixtures containing drug were placed in sealed aluminium 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 (FTIR)

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 4000-400 cm^{-1} .

X-Ray Diffractometry (XRD)

Powder X-ray diffraction patterns were recorded using Ni-filtered CuK α 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 2 θ angles of over 5 – 45°. The powder diffraction patterns of CAR, M β CD, physical mixture and inclusion complex were recorded.

Preparation of Buccal Tablets

CAR-M β CD complex equivalent to 6.25 mg of CAR was mixed with 7.5 mg of Carbopol 974P, 15 mg of sodium carboxymethylcellulose, 63.25mg of directly compressible lactose, 5 mg of PVPK30, 2 mg of talc and 1 mg of magnesium stearate. Tablets (100mg) were compressed using 9 mm flat beveled circular punches. In order to prevent drug release from tablet surface facing the oral cavity, the tablets were transferred to 10 mm die and a backing layer of 80 mg of ethyl cellulose was compressed on it.

In Vitro Drug Dissolution Studies

The dissolution studies of CAR alone, its physical mixture with M β CD and complex were conducted using USP XXIII dissolution apparatus type-II, at 37°C stirring at 50 rpm. Ten mg of CAR or its equivalent amount of CAR-M β CD binary mixture was added to 1000 ml of phosphate buffer pH 6.8 in order to maintain sink conditions. The samples were withdrawn at predetermined time intervals and analyzed spectrophotometrically at 285 nm. Dissolution studies of buccal tablets were performed using 900 ml of buffer, by sticking the ethyl cellulose layer side onto the paddle with the help of cyanoacrylate adhesive. All other parameters were similar to complex dissolution studies.

Porcine Buccal Tissue 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°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 tablet was 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°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 μ 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 Test⁸. 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

Differential Scanning Calorimetry (DSC)

FIG.1 shows the DSC scans for plain drug, M β CD and kneaded binary system. The plain drug showed sharp endothermic peak at 118 $^{\circ}$ C. M β CD showed a broad endothermic peak in the range of 100-120 $^{\circ}$ C due the release of water molecule. DSC thermogram of physical mixture was a mere superimposition of both the components.

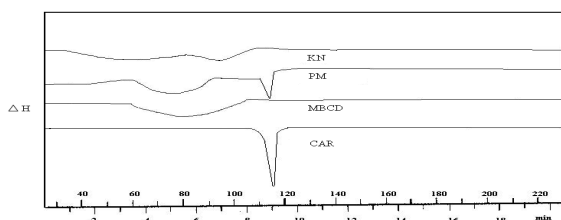


FIG.1 DSC Thermograms of CAR-M β CD system: Carvedilol (CAR), Methyl- β -cyclodextrin (M β CD), physical mixture (PM) and kneaded (KN) system

In case of kneaded binary system a shallow, less intense endotherm was obtained at 98 $^{\circ}$ C, with disappearance of endothermic

peak of CAR, suggesting complex formation. Miro *et al.*⁹ has reported a similar observation with CAR-hydroxypropyl- β -cyclodextrin complex.

Fourier Transformation Infrared Spectroscopy (FTIR)

FTIR spectra of CAR (FIG.2) showed characteristic bands at 1253, 1502 and 2922 cm^{-1} corresponding to aromatic secondary C-N vibrations, C-C multiple bond stretching and C-H stretching of aromatic ring respectively. FTIR spectra of physical mixture retained all the characteristic peaks of CAR. The kneaded binary system revealed disappearance of the characteristic peaks suggesting possible entrapment of carbazol moiety of CAR into the M β CD cavity.

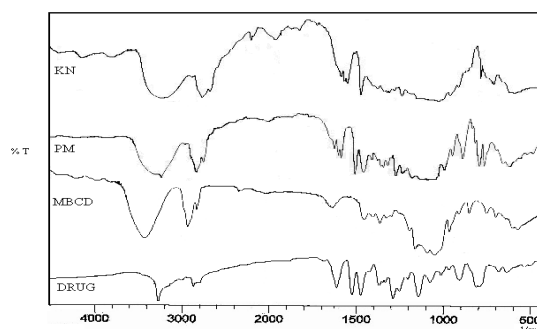


FIG. 2 FTIR spectra of CAR-M β CD system: Carvedilol (CAR), Methyl- β -cyclodextrin (M β CD), physical mixture (PM) and kneaded (KN) system

X-Ray Diffractometry (XRD)

CAR being a crystalline solid showed several sharp peaks in the XRD pattern [Fig.3]. M β CD being amorphous solid, showed two broad endothermic peaks. The XRD pattern of physical mixture was simply summation of the drug and M β CD. Disappearance of characteristic peaks of drug and appearance of two broad bands of much reduced intensities, in case of kneaded binary system, ensured formation of new amorphous entity. The results of characterization studies were confirming the inclusion complexation of CAR with M β CD.

In Vitro Drug Dissolution Studies

Dissolution patterns of plain drug, physical mixture with M β CD and kneaded binary system are presented in Fig.4. Incomplete release occurred from plain CAR in

3hr. M β CD being amorphous enhanced the wetting of CAR particles giving comparatively higher release rate from physical mixture.

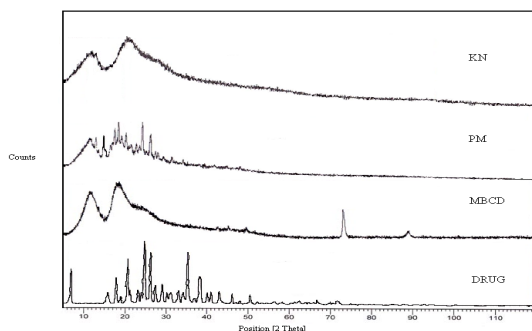


FIG. 3 X-Ray Diffractograms of CAR-M β CD system: Carvedilol (CAR), Methyl- β -cyclodextrin (M β CD), physical mixture (PM) and kneaded (KN) system

In case of kneaded binary system, complete release of CAR was obtained in 60 min. This further supported the formation of soluble inclusion complex between CAR and M β CD. Badaway *et al.* complexed Danazol with hydroxypropyl- β -CD and administered it buccally in the form of rapidly dissolving buccal patch to dogs¹⁰. It was observed that there was no improvement in bioavailability from this patch as compared to orally administered drug. This was attributed to swallowing of the patch indicating necessity to develop a formulation which will be retained on the buccal mucosa for sufficient time period. Hence it was decided to prepare buccal tablets of CAR.

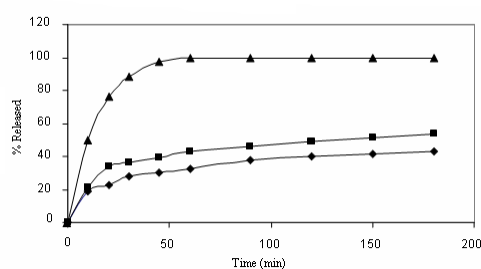


FIG.4 Dissolution profiles of CAR-M β CD system in phosphate buffer pH 6.8

(◆) CAR, (■) PM, (▲) KN

Initially various formulations of CAR were prepared to arrive at an optimum one which has good physical integrity and mucoadhesive strength (data not shown). The CAR- M β CD complex was then incorporated into this formulation instead of CAR. The dissolution pattern of buccal tablets was as shown in Fig.5.

Complete release of CAR occurred in 180 min from buccal tablets containing complexed CAR as compared to 40.23 % release from tablets containing plain drug. Han *et al.* has reported increase in release from disks containing nalbuphine enanthate- β CD system¹¹ and a similar observation was made by Guo for buccal patches containing buprenorphine- β CD system¹².

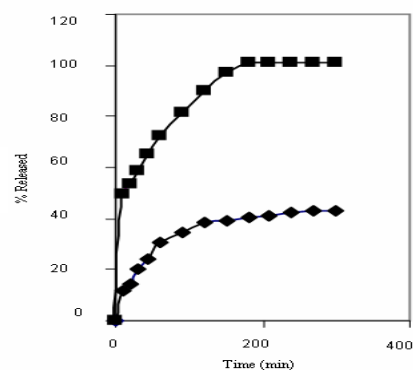


FIG.5 Dissolution profiles of CAR tablets in phosphate buffer pH 6.8

(◆) CAR, (■) CAR M β CD

This can be attributed to increase in drug concentration (diffusion driving force) inside the hydrated polymeric environment resulting in increased drug release rate. Thus it can be postulated that use of M β CD may increase concentration of drug in saliva ready for absorption.

Ex Vivo Drug Permeation Studies

Results of Ex vivo drug permeability studies of tablet containing plain drug and tablet containing complex were as shown in Fig.6. At the end of 5h, the amount of CAR permeated was 2.51 mg and 6.2 mg from plain tablets and tablets containing complexed drug respectively. The results were in accordance with the observation made by Jug *et al.* who reported increase in permeation of pyroxicam after complexation with HP β CD¹³. Thus the importance of M β CD not only in terms of increasing solubility of CAR but also in aiding its permeability across the buccal mucosa was highlighted.

Measurement of Mucoadhesive Force

Plain tablet showed good mucoadhesive strength of 18g which was in accordance with Varshosaz *et al.* who reported superior

bioadhesive properties for buccoadhesive nifedipine tablets containing carbopol¹⁴.

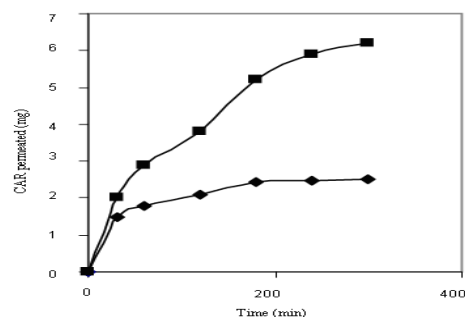


FIG. 6 Permeation through porcine buccal mucosa from tablets

(◆) CAR, (■) CAR MβCD

The mucoadhesive force remained unchanged for tablets containing complexed drug indicating no adverse effect of incorporation of MβCD on mucoadhesive properties.

Characterization of kneaded binary system revealed the formation of inclusion complex between CAR and MβCD which resulted in its improved solubility and dissolution rate. Buccal tablets containing complexed drug showed increased dissolution rate indicating higher concentration of drug in solution form as well as increased permeability through buccal mucosa. Thus it can be concluded that improvement in solubility by complexation along with avoidance of first pass metabolism by incorporation of complex into buccal tablet would lead to increased bioavailability of CAR.

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