INTERNATIONAL JOURNAL OF PHARMACEUTICAL, CHEMICAL AND BIOLOGICAL SCIENCES

Available online at www.ijpcbs.com

Research Article

FORMULATION AND EVALUATION OF BUCCOADHESIVE BILAYERED TABLETS OF CARVEDILOL

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ABSTRACT

The purpose of this research work was to establish mucoadhesive buccal tablets of carvedilol in the forms of bilayered tablets. The tablets were prepared using Hydroxy propyl methyl cellulose (HPMC K4M) and sodium carboxymethylcellulose (SCMC) and Carbopol-934 (CP) as bioadhesive polymers to impart mucoadhesion and ethyl cellulose (EC) to act as an impermeable backing layer. Buccal tablets were evaluated by different parameters such as weight uniformity, content uniformity, thickness, hardness, surface pH, swelling index, ex vivo mucoadhesive strength, in vitro drug release, and in vitro drug permeation. The mechanism of drug release was found to be non-Fickian diffusion (value of n between 0.5 and 1.0) for both the buccal tablets. The present study concludes that mucoadhesive buccal tablets of carvedilol can be a good way to bypass the extensive hepatic first-pass metabolism and to improve the bioavailability of carvedilol.

Key words: Bilayered buccal tablet, buccal delivery, mucoadhesion, carvedilol.

INTRODUCTION

Carvedilol, a nonselective beta-adrenergic blocking agent, is widely used in the treatment of hypertension, angina pectoris, and many other cardiovascular disorders. Although it is well absorbed in the gastrointestinal tract, its bioavailability is low (25%-35%) as a result of extensive first-pass metabolism. Since the buccal route bypasses the hepatic first-pass effect, the dose of carvedilol can be reduced. The physicochemical properties of carvedilol, its suitable half-life (5-7 hours), and its low molecular weight 495.81 make it a suitable candidate for administration by the buccal route.

In the present study, the objective was to prepare mucoadhesive buccal tablets of carvedilol to prolong the residence time of the buccal tablets, which ensure satisfactory drug release in a unidirectional fashion to the mucosa, and to avoid loss of drug resulting

from wash out with saliva. The buccal tablets were evaluated by weight uniformity, thickness, hardness, surface pH, swelling index, ex vivo mucoadhesive strength, In vitro drug release, and In vitro buccal permeation studies.

MATERIALS AND METHODS

MATERIALS

Carvedilol (99.96% purity), were gift samples from Dr.Reddy's Labs Ltd, Hyderabad, India. Hydroxy propyl methyl cellulose (HPMC K4M), Sodium carboxymethylcellulose (SCMC, 400 cps), Carbopol-934 (CP), ethyl cellulose and D-mannitol (S.D. Fine Chemicals, Mumbai, India) were obtained from commercial sources. All other reagents and chemicals used were of analytical reagent grade.

Preparation of Mucoadhesive Buccal Tablets[7]

Mucoadhesive buccal tablets containing carvedilol were prepared by direct compression method. The ingredients of the core layer (Table 1) were weighed accurately and mixed by trituration in a glass mortor & pestle. The mix was then compressed using 8mm die by a tablet press. In order to obtain constant tablet weight the manitol was added as filler excipient in the core layer. After compression of tablet the upper punch was removed carefully without disturbing the set up and mixed ingredients of the backing layer (Table 1) were added over the tablet and compressed again.

Evaluation parameters

Ex-vivo Mucoadhesive Strength[2]

A modified balance method was used for determining the ex vivo mucoadhesive strength. Fresh sheep buccal mucosa was obtained from a local slaughterhouse and used within 2 hours of slaughter. The mucosal membrane was separated by removing underlying fat and loose tissues. The membrane was washed with distilled water and then with phosphate buffer 7.4 saliva solution at 37°C.

The sheep buccal mucosa was cut into pieces and washed with phosphate buffer pH 6.8. A piece of buccal mucosa was tied to the glass vial, which was filled with phosphate buffer. The glass vial was tightly fitted into a glass beaker (filled with phosphate buffer pH 6.8, at 37°C ± 1°C) so that it just touched the mucosal surface. The buccal tablet was stuck to the lower side of a rubber stopper with cyanoacrylate adhesive. The two sides of the balance were made equal before the study, by keeping a 5-g weight on the right-hand pan. A weight of 5 g was removed from the right-hand pan, which lowered the pan along with the tablet over the mucosa. The balance was kept in this position for 5 minutes contact time. The water (equivalent to weight) was added slowly with an infusion set (100 drops/min) to the right-hand pan until the tablet detached from the mucosal surface. This detachment force gave the mucoadhesive strength of the buccal tablet in grams.

Swelling Study[7]

The swelling study of tables was determined by gravimetry. The swelling rate of the bioadhesive tablets was evaluated by using 1% agar gel plate. The average weight of the tablet was calculated (w_1). The tablets were placed on gel surface in a petridish placed in an incubator at 37±1ºC. Tablets was removed at different time intervals (0.5, 1.0, 2.0, 3.0, 4.0, 5.0), wiped with filter paper and reweighed (w_2). The swelling index was calculated by the formula.

$$\text{Swelling index} = (w_2 - w_1) / w$$

Surface pH Study[7]

The surface pH of the buccal tablets was determined in order to investigate the possibility of any side effects in vivo. As an acidic or alkaline pH may cause irritation to the buccal mucosa, it was determined to keep the surface pH as close to neutral as possible. The method adopted by Bottenberg et al was used to determine the surface pH of the tablet. A combined glass electrode was used for this purpose. The tablet was allowed to

swell by keeping it in contact with 1 mL of distilled water (pH 6.5 ± 0.05) for 2 hours at room temperature. The pH was measured by bringing the electrode in contact with the surface of the tablet and allowing it to equilibrate for 1 minute.

In vitro dissolution studies: [11]

The *in vitro* dissolution was carried out by using Tablets Dissolution Tester (USP-XXIII). The tablet is placed such that core faced to the dissolution medium (500 ml of 0.5% soidum lauryl sulphate). Dissolution medium temperature was maintained at 37°C and stirring at 50 rpm. An aliquot of the sample was periodically with drawn at suitable time intervals and the volume was replaced with fresh dissolution medium. The samples were analyzed spectrophotometrically at 242nm.

In Vitro Buccal Permation Studies[11]

In vitro buccal permeation of carvedilol from matrix tablets through the goat buccal membrane was studied. The membrane was mounted over a Franz diffusion cell of i.d. 2.1cm and the selected F2 and F5 formulations containing 6.25 mg of carvedilol was placed on the membrane. The receiver compartment of the diffusion cell was filled with 12.0 mL of alcohol: propylene glycol: phosphate buffer saline pH 7.4 mixture (40:15:45).The entire setup was placed over a magnetic stirrer and the temperature was maintained at 37°C by placing the diffusion cell in a water bath. One mL samples were collected at predetermined time intervals from the receptor compartment and replaced withan equal volume of the above mixture. The amount of carvedilol in the diffusion samples was estimated by the UV method.

RESULTS AND DISCUSSION

In the present work efforts have been made to develop mucoadhesive buccal tablets of carvedilol using direct compression technique involving mucoadhesive polymers like Carbopol, various cellulose ethers having different degree of solubility and swell ability, such as Hydroxy propyl methyl cellulose and Sodium carboxy methyl cellulose. Ethyl cellulose was selected as a backing material because this hydrophobic polymer has very low water permeability thus providing an impermeable backing layer that prevents drug loss. Magnesium stearate was included as anti adherent.

The FTIR spectral analysis showed that there was no appearance or disappearance of any characteristic peak, which confirms the absence of chemical interaction between drug and polymers.

The blend of ingredients was analyzed for physical characteristics. The angle of repose of formulation blends F_1 to F_6were in the range of 32º59' ± 1.464 to 33º20' ± 1.103. The bulk density, tapped density, Corr's index were found in the range of 0.433 to 0.317 gm/cc, 0.52-0.47gm/cc, and 16.66 – 14.28 respectively. It reveals that all the formulation blends were having good flow characteristics and flow rates. All the formulations pass the test for weight variation as per the IP standard ± 7.5 % deviation. Percentage of drug content for all formulations F_1 to F_6 was in the range of 96.1 ± 1.31 to 98.3 ±1.00 %.

Thickness of F_1 to F_6 formulations was found to be 0.128 to 3.35 ± 0.106 mm. Hardness of all formulations F_1-F_6 was found to be 5.2 ± 0.447 to 5.6 ± 0.548 kg/sq.cm.

The bioadhesion and drug release profile are dependent upon swelling behavior of the tablets. Swelling index was calculated with respect to time. The Swelling index was for all formulations F_1 to F_6 (After 4 hours) was in the range 1.119 ± 0.0346 to 1.120 ± 0.0370.

Buccal tablets of all the formulations Surface pH values in the range of 7.0 ± 0.10 to 7.4 ± 0.05 that indicates no risk of mucosal damage or irritation.

The bioadhesives property tablets of carvedilol containing varying proportions of polymers was determined with an insight to develop the tablets with adequate bioadhesiveness . The highest adhesion force and higest strength of the mucoadhesive bond was observed with the formulation as followed by $F_2$to F_5 containing carbopol 934 p and Hpmc k4m and carbopol 934 and Scmc respectively, Tablets of formulation F_1o F_6

containing HPMC k4 m and Scmc alone showed least adhesion force than tablet of all other formulation. The mucoadhesive strength of all the formulations F_1 to F_6 was found to be in the range of 9.2 ± 0.16 to 10.4 ± 0.54 gms.

The in vitro drug release of all the formulations F_1 to F_6 was found to be in the range of 93.02 ± 0.10 to 92.915 ± 053.Among the formulation studied F2 and F5 were found to be the best (F2 - CP-934-10mg, HPMC K4M-20mg, and mannitol-84.75mg as core layer and EC-45mg and Mag.Ste-5mg as backing layer and F5 -CP-934-10mg, SCMC-20mg, and mannitol-84.75 mg as core layer and EC-45mg and Mag.Ste-5mg as backing layer)

The formulation F2 showed 98.61±0.80 percentage of drug released at 12th hr with good swelling index and bioadhesion strength**.**

The formulation F5 showed 97.61±1.10 percentage of drug released at 12th hr with good swelling index and bioadhesion strength**.**

Both F2 and F5 formulations obeyed zero order kinetics with non-ficikan diffusion mechanism and showed these two formulations were taken as optimized formulations for in vitro buccal permeation studies.

Both Formulation F2 and F5 showed 86.90 ± 1.10 and 83.40 ± 0.85 respectively permeation drug through the buccal mucosa over a period of time 12th hrs.

Hence it can be conclusively stated the both F2 and F5 formulations necessary buccoadhesive property and the desirable release characteristics. However the detailed *In vivo* studies of the above formulations will through more light on their viability for consideration in the clinical practice.

All the formulations exhibited anomalous (non-ficikan transport) diffusion mechanism and follow zero order kinetic.

The values of n were estimated by linear regression of log (Mt/M_∞) versus log t, and these values were between 0.5 and 1.0, indicating that the release of carvedilol was found to be non-Fickian diffusion.

Table 1: Composition of Formulations of Mucoadhesive Buccal tablets

	Core Layer (mg)					Backing Layer (mg)	
Formula code	**Drug (mg)**	**CP-934**	**HPMC K 4M**	**SCMC**	**MANNITOL**	**EC**	**Mg.Ster**
F1	6.25	-	30	-	84.75	45	5
F2	6.25	10	20	-	84.75	45	5
F3	6.25	15	15	-	84.75	45	5
F4	6.25	15	-	15	84.75	45	5
F5	6.25	10	-	20	84.75	45	5
F6	6.25	-	-	30	84.75	45	5

Table 2: Physicochemical Properties of Bilayered Buccal Tablets of carvedilol*

Batch Code	Thickness (mm)	Hardness (kg/cm²)	% Drug Content	Surface pH	Muco -adhesiveStrength (g)
F1	3.34 ± 0.128	5.2 ± 0.447	96.1 ± 1.31	7.0 ± 0.10	9.8± 0.16
F2	3.36 ± 0.203	5.4 ± 0.548	99.4 ± 1.52	7.2 ± 0.23	16.0 ± 0.12
F3	3.40 ± 0.057	5.8 ± 0.447	98.5 ± 1.31	7.3 ± 0.10	14.0 ± 0.16
F4	3.39 ± 0.061	5.6 ± 0.548	97.1 ± 1.46	7.1 ± 0.11	12.0 ± 0.16
F5	3.50 ± 0.147	5.4 ± 0.548	97.8 ± 1.45	6.9 ± 0.10	15.0 ± 0.08
F6	3.35 ± 0.106	5.6 ± 0.548	98.3 ± 1.00	7.4 ± 0.05	10.4 ± 0.54

***Each value represents the mean ± SD of 3 determinations**

Table 3: In vitro dissolution studies for release kinetics

Formula Code	Drug release Kinetics						
	Zero order		First order		Higuchi	Peppa's	
	K_0	r	K_1	r	r	n	r
F_1	9.3036	0.99079	0.4429	0.732653	0.9804	0.66007	0.99994
F_2	8.17987	0.99571	0.369	0.856278	0.98607	0.76813	0.99652
F_3	9.44584	0.99561	0.1635	0.747604	0.98609	0.8558	0.9998
F_4	9.67705	0.99746	0.21105	0.855399	0.98477	0.85626	0.99693
F_5	10.323	0.99688	0.38107	0.891977	0.97015	0.82223	0.9971
F_6	8.6549	0.99617	0.31972	0.817707	0.96283	0.84842	0.99894

K_0- Zero order rate constant
r – Coefficient of Correlation
K_1- First order rate constant
n- diffusional exponent

Table 4: Invitro buccal permeation studies for release kinetics

Formula Code	Drug release Kinetics						
	Zero order		First order		Higuchi	Peppa's	
	K_0	r	K_1	r	r	n	r
F_2	9.2456	0.99079	0.4245	0.792653	0.9804	0.82007	0.99994
F_5	8.7864	0.99571	0.4576	0.856278	0.9807	0.76813	0.99852

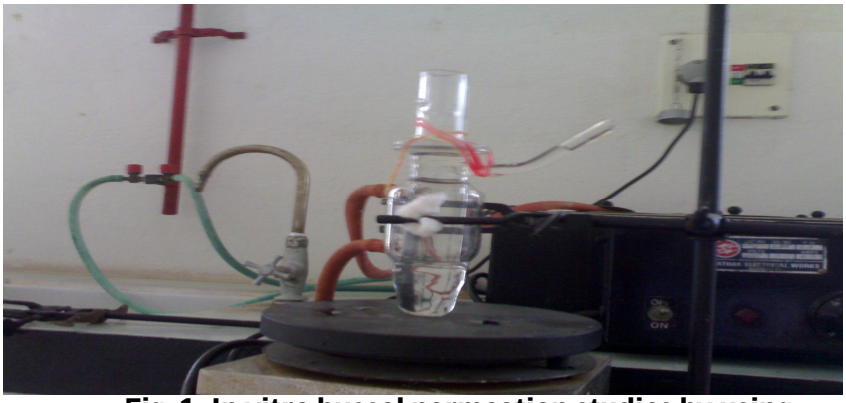

Fig. 1: In vitro buccal permeation studies by using Modified Franz Diffusion Cell

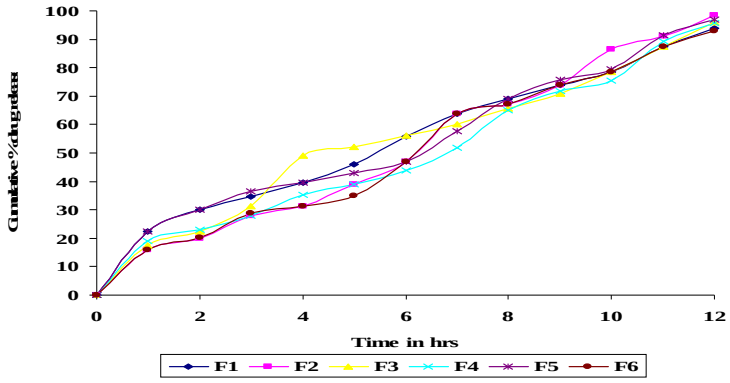

Fig. 2: Comparative invitro drug release profile for F1-F6 formulations

CONCLUSION

The mucoadhesive buccal tablets of carvedilol may be a good way to bypass the extensive hepatic first-pass metabolism and to improve the bioavailability of carvedilol through buccalmucosa.

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