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FORMULATION AND EVALUATION OF BILAYERED MUCOADHESIVE BUCCAL TABLETS OF CARVEDILOL

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ABSTRACT

The overall objective of present study was to formulate and evaluate bilayered mucoadhesive buccal tablets of Carvedilol using various bioadhesive polymers HPMCK100M, HPMCK4M, and carbopol. Ethyl cellulose was used as an impermeable backing membrane. The oral bioavailability of Carvedilol is (25% -35%) due to extensive first pass metabolism. Fourier Transform Infrared Spectroscopy analysis showed no evidence of drug excipients interaction. The formulations were prepared by direct compression and were evaluated for hardness, weight variation, drug content, surface pH, swelling studies, drug permeation, mucoadhesive strength and *in vitro* drug release. Physiochemical parameters like thickness (3.45-3.68 mm), weight variation (115.43-125.95 mg), hardness (53.2–65 N), friability (0.09–0.125 %) and drug content ((98.76–100.72%) were within the acceptable limits. The swelling index was reported to be in the range of 197.05–286.02 %, at 8 h. The surface pH of all the batches were in between 6.7 to 6.8. The mucoadhesive strengths (24.62–28.18 g) varied with the change in polymer concentrations especially of HPMC. From the data, it is evident that as the proportion of the polymer increases, the drug release was found to be reduced. In drug permeation study F3 showed slow and steady penetration of drug which resulted in 84 % at the end of 8 h. From this it is concluded that F3 showed promising results and Carvedilol bilayered mucoadhesive buccal tablets were prepared successfully using ethyl cellulose as a backing membrane.

KEYWORDS: Carvedilol, buccal tablet, ethyl cellulose, HPMC K100M, HPMC K4M, Carbopol.

INTRODUCTION

Buccal delivery of drugs provide an attractive alternative to the oral route of drug administration, particularly in overcoming deficiencies associated with the latter mode of administration problems such as high first pass metabolism, drug degradation in harsh gastrointestinal environment and this can be circumvented by administering a drug via buccal route.[1] In recent years, significant interest has been shown in the development of novel bioadhesive dosage forms for mucosal delivery of drugs that attempt to overcome these limitations. Drug absorption into the oral mucosa is mainly via passive diffusion into the lipoidal membrane. Compounds with partition coefficients in the range 40-2000 and pKa 2-10 are considered optimal to be absorbed through buccal mucosa. Compounds administered by buccal route include steroids, barbiturates, papain, and trypsin etc. Drugs can be absorbed from the oral cavity through the oral mucosa either by sublingual or buccal route.[2,3]

Various mucoadhesive polymers[4] (natural, semi-synthetic, and synthetic) used in this delivery system become adhesive on hydration, therefore can be used for targeting a drug to a particular region of the body. Initially, when the mucoadhesive product is in contact with the mucosal membrane, it swells and spreads, initializing deep contact with the mucosal layer and then mucoadhesive materials (polymers) are activated by the presence of moisture and drug releases slowly.[5]

Mechanism of bioadhesion can be described in three successive steps[6,7]

1. Wetting and swelling of polymer to permit intimate contact with biological tissue.
2. Interpenetration of bioadhesive polymer chains and entanglement of polymer and mucin
3. Formation of weak chemical bonds between entangled chains.

Hypertension is a condition in which the force of the blood against the artery walls is too high. Long-term high blood pressure, however, is a major risk factor for coronary artery disease, stroke, heart failure, atrial fibrillation, peripheral arterial disease, vision loss, chronic kidney disease and dementia.[8,9] Carvedilol is a non-selective β-adrenergic blocking agent with α1-blocking activity. It has vasodilating activity at alpha-1 receptors. It also possesses antioxidant and antiproliferative effects, which may enhance its ability to combat the deleterious effects of sympathetic nervous system activation in heart failure. It is used in the management of hypertension and angina pectoris, and as adjunct to standard therapy in symptomatic heart failure. The bioavailability of Carvedilol is 25% -35 % as it undergoes stereo-selective first-pass metabolism. Since the buccal route bypass the first pass

metabolism, its bioavailability can be increased. The half-life of Carvedilol is 7-10 hours. Carvedilol is a weak base with pKa value 7.7 – 7.9 and log P (partition coefficient) value of 3.9, which indicates sufficient lipophilicity to pass through any biological membrane, including buccal membranes.[10-12] The main objective of the study is to prepare the bilayer buccal tablet of Carvedilol which helps to overcome the bioavailability related problem.

MATERIALS AND METHODS

Materials: Carvedilol was a gift sample from Dr.Reddy's Laboratories Ltd., Hyderabad, India. HPMC K100M, HPMCK4M and Carbopol (Colorcon Asia Pvt Ltd., Goa), Ethyl cellulose (Sigma Aldrich Fine Chemicals Ltd.,), Lactose, Aspartame (Fonterra Excipients GmbH & Co.) Povidone K30 (Nanhang Industrial Company Ltd., China), Isoproply alcohol (Chemspure, Chennai), Magnesium stearate (Lobachemie Pvt.Ltd, India), Talc (S.D. Fine Chemical Ltd., Mumbai) were obtained from commercial sources.

Methods

Development of standard curve of carvedilol: 50 mg of Carvedilol was dissolved in 50 ml of methanol. Aliquots were withdrawn from the standard stock solution, appropriate dilutions were made with pH 6.8 phosphate buffer to obtain concentrations in the range from 2 to 10 µg/ml. The spectrum was recorded, absorbance was measure at 242 nm and a calibration curve was plotted.

Drug excipients compatibility study by Fourier transform infra red spectroscopy: The compatibility of drug and excipients is an important prerequisite before formulation. It is therefore necessary to confirm that the drug does not react with the polymers and excipients under experimental conditions and affect the shelf life of product or have any other unwanted effects on the formulation. Drug and excipients compatibility was studied using FTIR spectral analysis.

The I.R spectrum of Carvedilol and physical mixtures of Carvedilol with polymers were recorded using Fourier Transform Infra Red Spectroscopy (IRT Racer-100). The spectrum was scanned over a frequency range of 400-4000 cm^{-1} and the resultant spectra were compared for any spectral changes.

Preparation of carvedilol buccal tablet: Mucoadhesive buccal tablets containing Carvedilol were prepared by direct compression method. The ingredients of the core layer (Table 1)

were weighed accurately. All the powders except lubricants were passed through 80 mesh and mixed by trituration in a glass mortor and pestle. Lubricants were passed through #80 mesh and added to the above mixture and blended for 2 min in a polythene bag. The mixture was then compressed using a 6.35 mm diameter die in a single stroke multi-station tablet machine. After compression of tablet the upper punch was removed carefully without disturbing the set up and mixed ingredients of the backing layer were added in each die over the tablet and compressed again to form mucoadhesive bilayer tablets.

Table 1: Composition of mucoadhesive buccal tablets.

Ingredients (mg)	F1	F2	F3
Core layer Carvedilol	3.125	3.125	3.125
HPMC K100 M	12.5	15	17.5
HPMC K 4 M	7.5	10	12.5
Carbopol	10.0	15	20
Lactose	40	40	40
Aspartame	2.0	2	2
Magnesium stearate		2.875	2.875
Talc	2	2	2
Color			
Backing layer			
Ethyl cellulose	30	30	30
Magnesium stearate	4.5	4.5	4.5

Evaluation of tablet properties: Different quality control parameters of all the batches of mucoadhesive Carvedilol tablets were analyzed by adopting the method as described.[13]

Thickness: The tablets were evaluated for their thickness using a vernier caliper (Mitutoyo, Japan) measured in terms of micrometer. Average of three readings were taken and the results were tabulated (n = 3).

Uniformity of weight: Twenty tablets (n = 20) of each batch were selected and weighed collectively and individually. From the collective weight, average weight was calculated. Each tablet weight was then compared with average weight to ascertain whether it was within the permissible limits or not.

Friability: Twenty tablets (n = 10) of each batch were weighed and put into the friabilator drum. After 100 revolutions of friabilator, tablets were recovered. The tablets were then freed from dust and weighed. Friability was calculated using the formula

$$\% \text{ Friability} = \frac{\text{Initial wt of tablets} - \text{Final wt of tablets}}{\text{Initial wt of tablets}} \times 100$$

Hardness: Twenty tablets (n = 20) were taken for the hardness test using a hardness tester. The tablet was placed between the two probes, of which, one is a movable probe and another is an immovable probe of the hardness tester. Then the force was applied from the movable probe. The force to break the tablet was recorded, which was taken as the hardness of the tablet.

Surface pH: The surface pH[14] of the buccal tablet was determined in order to investigate the possibility of any side effects *in vivo*. As an acidic or alkaline pH may irritate the buccal mucosa, it is necessary to keep the surface pH as close to neutral as possible. A combined glass electrode was used for this purpose. The tablet was allowed to swell by keeping it in contact with 1 ml of phosphate buffer pH 6.8 for 2 h at room temperature. The pH was identified by bringing the electrode into contact with the tablet surface and allowing it to equilibrate for 1 min.

Swelling study: The swelling index of the mucoadhesive tablets of Carvedilol were evaluated using a 1% w/v agar gel plate.[15-16] An agar gel plate was chosen as the simple model of the mucosa as it resembles the secreting fluid in and around the buccal mucosa required for bioadhesion and subsequent swelling of the formulation to provide adequate release of the drug.

Four tablets of every batch were weighed and then kept on the agar gel plate surface in petri dishes, which were placed in an incubator at 37°C±0.1°C. Then, the swollen tablets were weighed at different intervals; the excess water on the surface of tablets was removed by using filter paper. The average weight was calculated and the swelling index was calculated by the formula,

$$\text{Swelling Index (S.I.)} = \frac{W_t - W_o}{W_o} \times 100$$

where,

S.I. = swelling index

W_t = average weight of tablet at time t

W_o = average weight of dry tablet before placing on the agar plate

Drug content: Twenty tablets from each batch were weighed accurately and powdered powder equivalent to 10 mg of Carvedilol was shaken with methanol in 50 ml volumetric flask and from this standard solution 4 ml was pipette out and then diluted up to 100 ml with phosphate buffer (pH 6.8). Resulting solution was filtered and the absorbance of filtrate was recorded on spectrophotometer at 242 nm and content of Carvedilol was calculated.

***In vitro* drug release study:** In vitro dissolution studies of buccal tablets of Carvedilol were carried in dissolution test apparatus-II employing a paddle stirrer at 50 rpm using 900 ml of pH 6.8 phosphate buffer as dissolution medium. One tablet was used from each batch. The release study is performed at 37±0.5˚C. The backing layer of the buccal tablet was attached to glass disk with cyanoacrylate adhesive. Samples of 5 ml from each batch was withdrawn at predetermined time intervals and replaced with the fresh medium. The samples were filtered through membrane filter disc and analysed for Carvedilol after appropriate dilution by measuring the absorbance at 242 nm in U V spectrophotometer. The % drug release was calculated.

***Ex vivo* drug permeation study:** Diffusion study of pure drug was carried out using fresh sheep oral mucosa tissue, which was procured from local slaughterhouse and placed in Krebs buffer pH 7.4. Isolation of the epithelium was done mechanically by using scissors and forceps. The studies were carried out using Franz's diffusion cell. It consists of upper cylindrical compartment open from above and containing the sheep buccal mucosa at its base. Lower compartment was in form of a closed cylinder having the sampling port and had Teflon coated magnetic bead at the base. The junction between two compartments was designed in such a manner that the buccal membrane did not shift from its place. The receptor compartment was filled with required volume of phosphate isotonic buffer pH 6.8 maintained by placing Teflon coated magnetic bead at the base in a uniform speed. The whole assembly was maintained at 37˚C±1°C. The withdrawn samples was then diluted suitably, then assayed spectrophotometrically at 242 nm, and the % drug diffused was calculated.

Mucoadhesion strength: Mucoadhesion strength[17] of the tablet was measured on a modified physical balance using sheep buccal mucosa as model mucosal membrane. Fresh sheep buccal mucosa was obtained from a local slaughter house and was used within 2 hrs of slaughtering. The mucosal membrane was washed with distilled water and then with phosphate buffer pH 6.8. A double beam physical balance was taken and to the left arm of balance a thick thread of suitable length was hanged and to the bottom side of thread a glass

stopper with uniform surface was tied. The buccal mucosa was tied tightly with mucosal side upward using thread over the base of inverted 50 ml glass beaker which was placed in a 500 ml beaker filled with phosphate buffer pH 6.8 kept at 37°C. The buccal tablet was then stuck to glass stopper from one side membrane using cyanoacrylate adhesive. The two sides of the balance were made equal before the study, by keeping a weight on the right hand pan. A weight of 5 g was removed from the right hand pan, which lowered the glass stopper along with the tablet over the mucosal membrane with a weight of 5 g. The balance was kept in this position for 3 min. Then, the weight was increased on the right pan until tablet just separated from mucosal membrane. The excess weight on the right pan i.e. total weight minus 5gm was taken as a measure of the mucoadhesive strength. The mean value of three trials was taken for each set of formulations. After each measurement, the tissue was gently and thoroughly washed with phosphate buffer and left for 5 minutes before placing a new tablet to get appropriate results for the formulation. After calculating mucoadhesion strength the force of adhesion are calculated using equations

$$\text{Force of Adhesion (N)} = \frac{\text{Mucoadhesive strength} \times 9.8}{1000}$$

RESULTS AND DISCUSSION

Calibration curve of carvedilol: The calibration curve of Carvedilol in phosphate buffer 6.8 was derived from the concentration and corresponding absorbance. Values of linear regression analysis gave the equation for the line of best fit as y = 0.0022x + 0.0012. Linearity was observed in the concentration range between 2 to 10 µg/ml. The r^2 value is 0.997 and represented graphically in Fig.1.

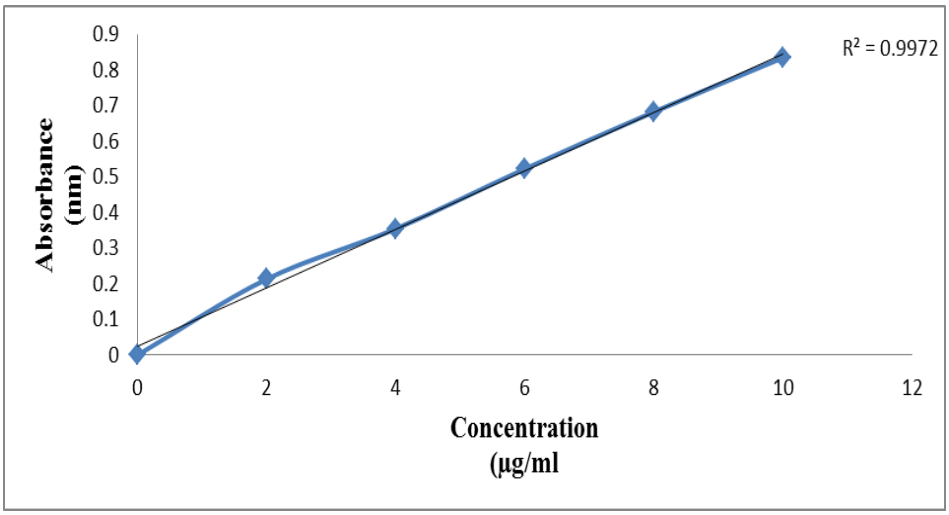

Fig. 1: Calibration curve of carvedilol.

Drug –excipient compatibility (FT-IR) study of carvedilol: Drug–Excipient compatibility study by FTIR study: Based on the FTIR interpretation results, all the major drug peaks were identified when compared with the physical mixture of drug and polymer, which ensures that there was no any chemical interaction between them. The major sharp and significant peaks (functional groups) of the drug was found to be in the wave numbers of 3547.2 showing N-H stretching, 2995 and 2923 showing C-H stretching, 1683 showing C=C stretching, 1252 showing C-C stretching and 1099 showing C-H deformation (Fig. 2-4)

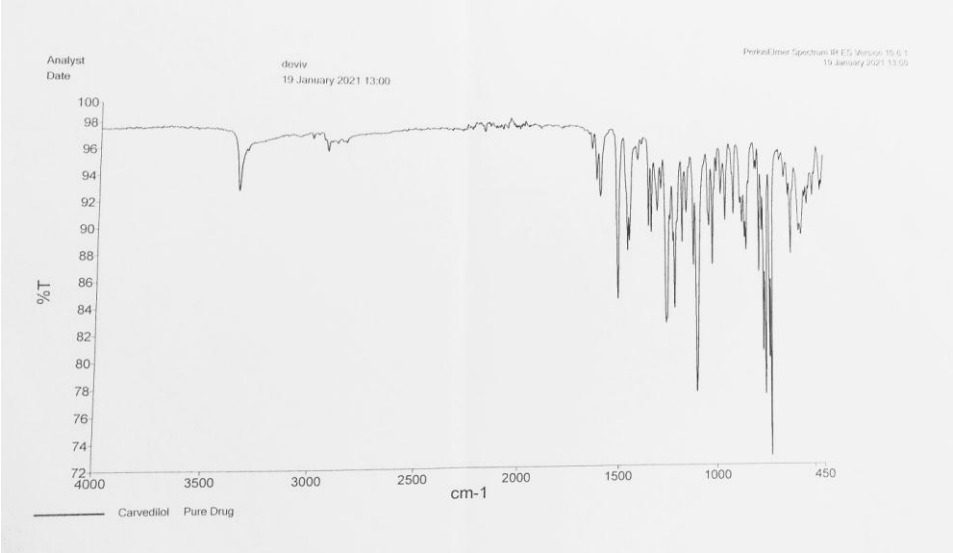

Fig. 2: FTIR of carvedilol.

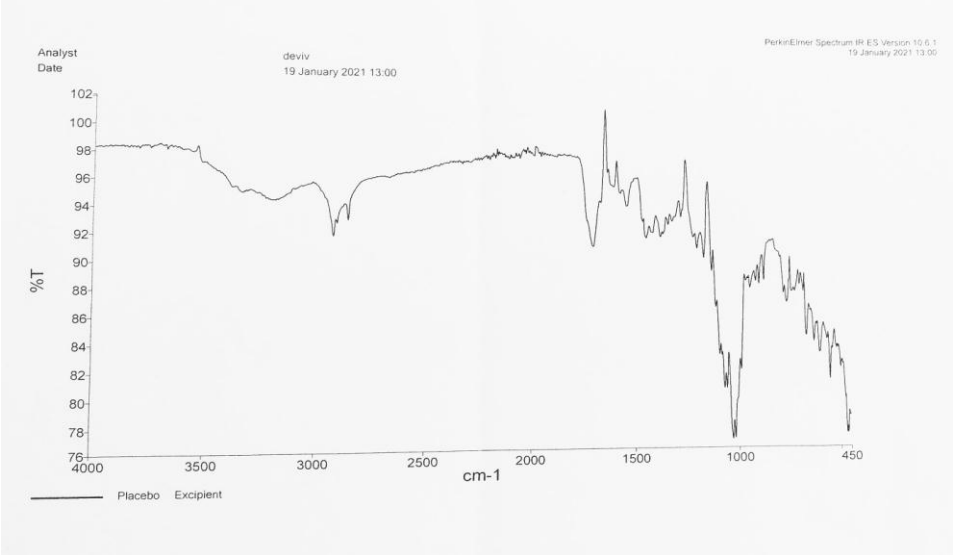

Fig. 3: FTIR of HPMC.

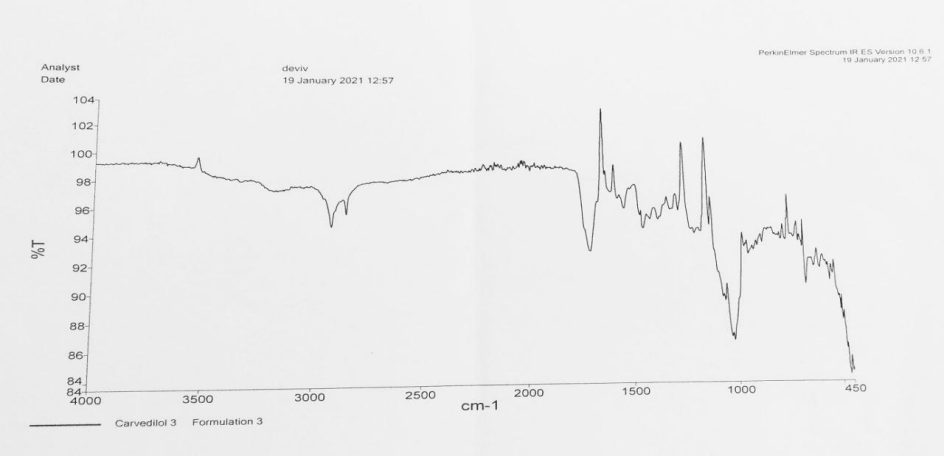

Fig. 4: FTIR of Carvedilol + excipients.

All the physical parameters evaluated after compression of Carvedilol mucoadhesive buccal tablets were found to be satisfactory. Typical tablet defects, such as capping, chipping and picking, were not observed. The physicochemical characterizations of different batches of tablets are given in Table 2. The average thickness of the tablets ranged between 3.45±0.18 to 3.68±0.09 mm and all the formulations were within acceptable limits. All the batches showed uniform thickness. Weight variations for different formulations were found to be 115.43±1.14 to 125.95±1.30 mg.. The average percentage deviation of all tablet formulations was found within the limit, and hence all formulations passed the test for uniformity of weight as per official requirement. The hardness of all the Carvedilol buccal tablets formulations were ranged from 53.2±2.03 to 65±1.08 N that were according to the specification. The percentage friability of all the formulations were ranged from 0.09±0.07% to 0.125±0.05 % and found within the prescribed limits. The percentages of drug content of the entire formulations were found between 98.76±1.72 to 100.72±1.98 which were within the acceptable limits.

Table 2: Evaluations of carvedilol buccal tablets.

Formulation	Thickness (mm)	Hardness (N)	Friability (%)	Uniformity of weight	Surface pH	Drug content
F1	3.45±0.18	53.2±2.03	0.125±0.05	115.43±1.14	6.7±0.05	100.72±1.98
F2	3.63±0.09	59.1±0.14	0.102±0.12	120.68±1.5	6.7±0.05	99.69±2.05
F3	3.68±0.13	65±1.08	0.090±0.07	125.95±1.30	6.8±0.05	98.76±1.72

Swelling study: Swelling index is an important parameter in judging the mucoadhesion property, at least in the initial stages, since water uptake is important for the polymers to uncoil and interact with the mucin. The swelling index of the formulations of Carvedilol tablets were determined using agar plate at different time intervals of 1, 2, 4 and 8 h and

results are depicted in Fig 5 and Table 3. All the formulations showed an appreciable increase in swelling index and achieving maximum swelling effect at 8 h. The formulation that contains higher concentration of HPMC K4M, HPMC 100M and carbopol showed higher swelling indices due to higher hydrophilicity and more water uptake of the polymers. The tablets did not show any significant change in their morphological shape and form, throughout the study. The highest swelling was shown by the batch F3 i.e. 286.02 % with higher concentration of HPMC and carbopol whereas the lowest swelling behavior was shown by the batch F1 at 197.05 %.

F1 **F2** **F3**

Fig. 5: Swelling study of carvedilol buccal tablets in 8th hour.

Table 3: Comparative study of swelling index.

Formulations	Swelling Index (%)			
	1 hr	2 hr	4 hr	8 hr
F1	87.82±0.38	137.18±0.20	164.24±0.08	197.05±0.10
F2	98.59±0.56	1560.18±0.28	192.05±0.06	238.31±0.07
F3	102.15±0.22	188.29±0.44	221.21±0.34	286.02±0.08

***In vitro* dissolution studies release:** To explore the effect of polymer composition and proportion in drug release behavior, the *in vitro* dissolution study of formulated batches of mucoadhesive tablets was carried out and the results are presented in Fig. 6.

From the data, it is evident that as the proportion of the polymer increases, the drug release was found to be reduced. Among the three formulations F1 shows 100% release in the 8th hour, whereas F2 shows 96 % release at the end of 8th hour. F3 shows 86 % release at the end of 8th hour. It indicates that sustained release of drug can be obtained by increasing the proportion of HPMC K4M, HPMC K100M and carbopol. Due to usage of polymer HPMC K4M the drug release was controlled during the 1st h. The drug release was gradually increased according to time.

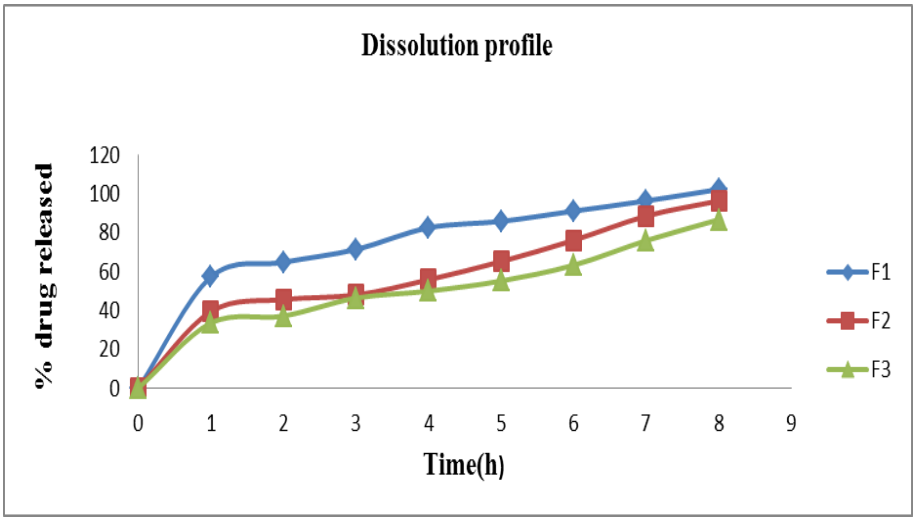

Fig. 6: Dissolution profile of different batches of carvedilol buccal tablets.

***Ex vivo* permeation studies:** The diffusion study was performed using Franz diffusion cell apparatus. The oral mucosa of sheep resembles that of humans more closely in terms of structure and composition and therefore sheep mucosa was selected for drug permeation studies. The studies were done for 8 h for all the formulations. The result reveals that Carvedilol was released from the formulation and penetrated through the sheep buccal membrane and could possibly penetrate through the human buccal membrane. The results are shown in Fig.7. Among the three formulations F1 showed 35.2 % penetration of drug in the 1st h and 95 % at the end 8th hour. F2 showed a more consistent increase in penetration of drug with 23% at 1st hr and 97% at the end of 8th hour. F3 showed 82 % at the end of 8th hour. In diffusion study polymer played a crucial role which indicates that sustained release of drug can be obtained by increasing the proportion of polymers such as HPMC K4M, HPMC K100M and carbopol. Due to usage of polymer HPMC K4M the drug penetration was controlled by giving slow and steady results. The results indicated that the *in vitro* and *ex vivo* techniques correlation was good.

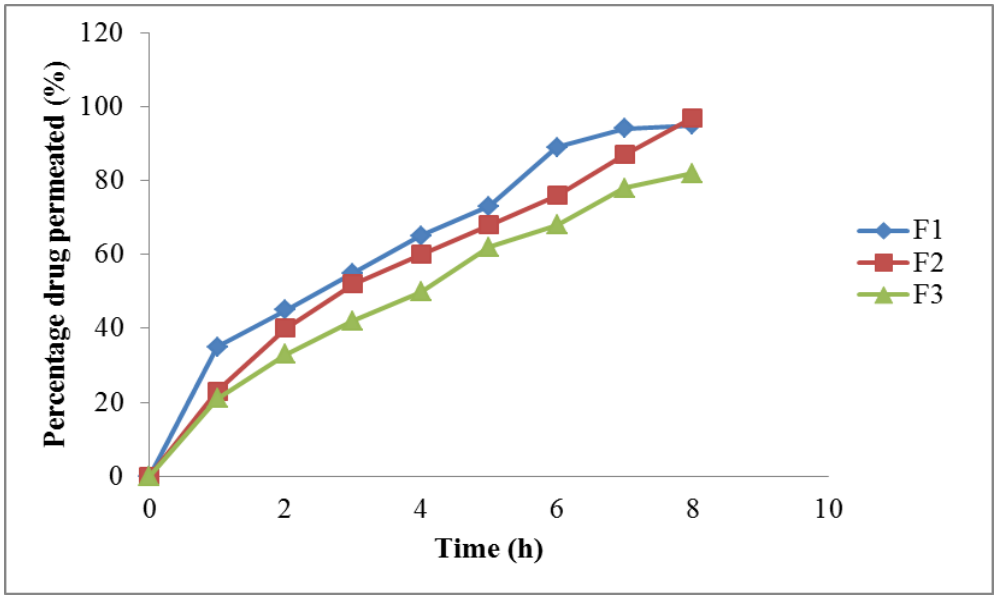

Fig. 7: Permeation profile of different batches of carvedilol buccal tablets.

Mucoadhesive strength: The in vitro mucoadhesive strength study was performed. On the modified pan balance, the force required to detach the tablet from the porcine buccal mucosa was recorded. The mucoadhesive properties were reported to be influenced by the nature and amount of bioadhesive polymers used in the formulation. As the increase in the content of HPMC K100M, bioadhesive strength also increased.It may be due to the rapid swelling and forming matrix which helps in bioadhesion of the drug. All the formulation showed good mucoadhesive strength. In this study, the mucoadhesive strength of the formulations was reported to be prominently influenced by the concentration of HPMC. The lowest value was reported in F1 (24.62 g) in which the lowest proportion of HPMC was incorporated. Similarly highest value was reported in F3 (28.18 g) which has the highest amount of HPMC. The force of adhesion was calculated using bioadhesive strength. These results are shown in the Table 4.

Table 4: Mucoadhesive strength and force of adhesion of carvedilol buccal tablets.

Formulations	Mucoadhesive strength (g)	Force of adhesion (N)
F1	24.62±0.25	0.241±0.007
F2	25.46±0.16	0.249±0.001
F3	28.18±0.06	0.276±0.001

CONCLUSION

Transmucosal buccal route of delivery for carvedilol is one of the best alternatives as it would bypass the extensive first pass metabolism and thus the dose can also be reduced and

bioavailability improved. Formulation F3 exhibited a good balance between *in vitro* release, *ex vivo* drug permeation, mucoadhesion strength and was therefore selected as the optimized formulation. The optimized formulation was also satisfactory in terms of surface pH and physical parameters. The formulations of Carvedilol mucoadhesive tablets can be an effective alternative route to prevent the first-pass effect and to improve the bioavailability through the mucosal membrane. It can also enhance patient compliance by fascinating extended release of the drug.

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