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Research Article

DEVELOPMENT AND EVALUATION OF MUCO-ADHESIVE BILAYER BUCCAL TABLET OF CARVEDILOL

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ABSTRACT
Carvedilol, a non-selective α/β antagonist has been comprehensively utilized in the management of cardiovascular disease, stable heart disease and symptom cardiopathy. Aim of present study was to develop and assess mucoadhesive bilayer buccal tablets of carvedilol implementing Guar gum, Xanthan gum and sodium alginate (Na-alginate) as the mucoadhesive polymers and ethyl cellulose as a rubberized backing layer to prevail bioavailability issue, to diminish dose dependent side effects and frequency of administration. to check the role of various compound as mucoadhesive, total eight batches (F1-F8) were formulated and further evaluated for micromeritics, thickness, hardness, friability, weight variation, surface pH, mucoadhesive strength, swelling index, ex vivo mucoadhesion and in vitro drug release study. Blend of all batches (F1-F8) showed excellent flow properties. The surface pH of all tablets was found to be satisfactory (6.1-6.6). Batch F4 was optimized on the basis of high bioadhesive strength (14.09±0.21). F4 extended the drug release up to 8 hours (77.46%) and followed zero order release kinetics (R^2 value0.9986). Hence it can be concluded that systemic delivery of carvedilol can be enhanced by formulating it into mucoadhesive dosage form using guar gum and Na-alginate together.

Keywords: *Carvedilol; Guar Gum; Na-alginate; Buccal Tablet*

INTRODUCTION
Although drugs can be administered though several different routes to produce desired pharmacological action, till today oral route is most prominent and preferable route of drug administration (Kumar *et al.*, 2012). Noteworthy, though oral route offers patients compliance, it has some disadvantages like hepatic first-pass metabolism or instability in the acidic environment (Gavini *et al.*, 2002). So the quest to improve the effectiveness of drug trough oral route diverts the research group towards utilization of various transmucosal routes (i.e. the mucosal linings of the oral, vaginal, nasal, and rectal) for drug delivery. Buccal delivery facilitates direct entry of drug into the systemic circulation, avoids the hepatic first-pass effect, and ultimately protects the drug from destructive acidic environment of the stomach (Sojaei *et al.*, 2001).
Adhesion as a process refers to the fixing of two surfaces to one another (Kinloch, 2001). While, if adhesion occurs on mucosal membranes it is generally termed mucoadhesion (Henriksen *et al.*, 1996). To elicit the desired therapeutic response, a buccal drug delivery system should have good bioadhesive properties, so that it can remain unaffected in the oral cavity for the required period. To achieve this myriad mucoadhesive polymers such as Carbopol, Polycarbophil, Polyacrylic acid, hydroxyethylcellulose and so on are extensively used (Punita and Girish, 2010).
Carvedilol, a non-selective α1, β1, β2 -adrenergic antagonist has been extensively used in the management of hypertension and stable angina pectoris. Carvedilol slows the heart rhythm and reduces the force of the heart's pumping and ultimately reduces the workload of the heart (Stafylas and Sarafidis, 2008). As compare to other beta blockers, carvedilol has negligible inverse agonist activity (Vanderhoff *et al.*, 1998).
Due to extensive first pass metabolism the bioavailability of carvedilol is low (approximately 25%).[9] Literature study reveals that Attempt has been previously made for formulation of Mucoadhesive Bilayer Buccal tablets of carvedilol (Wadageri *et al.*, 2012; Murthy *et al.*, 2013). Hence in present work an attempt has been made to develop mucoadhesive bilayer buccal tablets of carvedilol using Guar gum,

Xanthan gum and sodium alginate (Na-alginate) as the mucoadhesive polymers and ethyl cellulose as an impermeable backing layer.

MATERIALS AND METHODS

Material

Carvedilol was kindly provided as a gift sample from Zydus cadila (Mumbai, India). Guar gum and Xanthan gum was purchased from Lucid Group (Mumbai, India). Sodium alginate, Mannitol, PVP K30, PEG 6000, Talc, Ethyl cellulose and Magnesium stearate were purchased locally and rest chemicals were of analytical grade.

Methods

Preparation of Physical Mixture of Buccal Tablet of Carvedilol

All the ingredients including drug, excipients and polymer were weighed accurately according to the batch formula (Table 1). The drug is thoroughly mixed with mannitol on a butter paper with the help of a stainless steel spatula. Further all the ingredients except lubricant were mixed in the order of ascending weights and blended for 10 min in a polyethylene pouch. After uniform mixing of ingredients, lubricant was added and again mixed for 2 min (Panday *et al.*, 2010).

Table 1: Composition of Mucoadhesive Bilayer Buccal Tablet

Ingredients	F1	F2	F3	F4	F5	F6	F7	F8
Carvedilol	6.25	6.25	6.25	6.25	6.25	6.25	6.25	6.25
Guar gum	20	20	30	40	…	…	…	…
Xanthan gum	…	…	…	…	20	20	30	40
Sodium alginate	…	15	15	15	…	15	15	15
PVP k30	5	5	5	5	5	5	5	5
PEG 6000	2	2	2	2	2	2	2	2
Mannitol	…	44.75	34.75	24.75	…	44.75	34.75	24.75
Magnesium stearate	2	2	2	2	2	2	2	2
Talc	5	5	5	5	5	5	5	5
Ethyl cellulose	50	50	50	50	50	50	50	50

** Weights expressed as mg per tablet*

Preformulation Studies of Physical Mixture

Compatibility Studies

Fourier transform Infrared (FTIR) analysis:

IR study was carried out to check compatibility between Carvedilol and all excipients. FTIR spectra of purified drug and excipients were recorded using an infrared spectrophotometer (Shimadzu- 8400S). The baseline correction was done using dried potassium bromide. Uniformly mixed sample of carvedilol and potassium bromide were kept in a sample holder and a spectrum was recorded over the wave number 400-4000 cm^{-1}.

Flow Properties

Different micromeritic properties such as angle of repose, Carr's compressibility index and Hausner's ratio were used to characterize the flow properties of physical mixture of mucoadhesive bilayer buccal tablet.

Angle of repose:

Angle of repose for blend of each formulation (Batch F1-F8) was determined by fixed funnel method. The funnel was kept at fixed height h, above a plane of paper kept on a flat horizontal surface. Angle of repose was determined by following eqn (Jadhav *et al.*, 2014).

$$\theta = \tan^{-1}(h/r) \qquad [1]$$

Where, 'θ' is the angle of repose; h is height between the lower tip of the funnel and the base of the heap of blend; and r is radius of the base of heap formed.

Carr's Compressibility Index (CCI) and Hausner's Ratio (HR):

It is used to evaluate flowability of powder by comparing the bulk density and tapped density of a powder. Bulk density and tapped density was determined by using the bulk density apparatus Lab Hosp, (Mumbai, India).[13]

$$\mathrm{CCI} = \frac{(\mathrm{TD} - \mathrm{BD})}{\mathrm{TD}} \mathrm{X}\ 100 \qquad [2]$$

$$\mathrm{HR} = \frac{\mathrm{TD}}{\mathrm{BD}} \qquad [3]$$

Where, TD is tapped density; and BD is bulk density.

Preparation of Bilayer Buccal Tablet of Carvedilol

The prepared blend (100 mg) of each formulation was pre-compressed, on a 10-station rotary tablet punching machine (Clit, Ahmadabad) at a pressure of 0.5 ton and turret speed of 2 rpm to form single layered flat-faced tablet of 7 mm diameter. Then, 50 mg of ethyl cellulose powder was added and final compression was done at a pressure of 3.5 tons and turret speed of 2 rpm to get bilayer tablet.

Evaluation Studies of Carvedilol Buccal Tablets

Hardness

Tablets should be sufficiently hard to resist breaking during normal handling and yet soft enough to disintegrate properly after swallowing .The hardness of tablets measured by Monsanto hardness tester. The hardness was measured in terms of kg/cm^2 (Satyabata *et al.,* 2010).

Thickness

3 tablets from each batch of formulation were collected and the thickness of the tablets was measured with the help of vernier caliper. The average thickness was calculated (Raman *et al.,* 2007).

Friability

Roche friability test apparatus was used to determine the friability of the tablets. Twenty pre-weighed tablets were placed in the apparatus and operated for 100 revolutions and then the tablets were reweighed. The percentage friability was calculated according to the following equation (Jadhav *et al.,* 2013).

$$\%\ \text{Weight loss} = \frac{\mathrm{Wo} - \mathrm{Wt}}{\mathrm{Wo}} \times 100 \qquad [4]$$

Where, Wo and Wt are initial weight and final weight after time t, respectively.

Weight Variation

Randomly selected twenty tablets form each batch (F1-F8) were subjected to weight variation test as per Indian Pharmacopoeia 2007. Each tablet was weighed individually to calculate the average weight and then percent variation in each tablet was calculated (IP 2007).

Drug Content

Three tablets (Equivalent to 10 mg) from each batch were taken in separate 100 mL volumetric flaks containing 100 ml of phosphate buffer pH 6.8 containing 20% methanol and were kept for 24 hrs under constant stirring. The solutions were then filtered, diluted suitably with the solvent and analyzed at 241 nm using UV spectrophotometer. The average of three tablets was considered as the content of drug in one tablet unit (IP 2007).

Surface pH

Tablets were allowed to swell by keeping it in contact with 1 ml of distilled water (pH 6.5 ± 0.05) for 2 hr at room temperature. Further the pH was measured by bringing the electrode in contact with the surface of the tablet and allowed it to equilibrate for 1 min (Panday *et al.,* 2010).

Ex vivo Mucoadhesive Strength

The equipment used for testing bioadhesion was assembled within the laboratory. Mucoadhesion strength of the tablet was measured on a changed physical balance using the method described by Gupta *et al* with bovine cheek pouch as model mucosal membrane (The buccal mucosa was collected from the local slaughterhouse) (Wadageri *et al.,* 2012; Gupta *et al.,* 1992).

A double beam physical balance was taken, the left pan was removed. To left arm of balance a thick thread of appropriate length was hanged. To the bottom side of thread a glass stopper with uniform

surface was tied. A clean glass mortar was placed below hanging glass stopper. In this mortar was placed a clean 500 ml glass beaker, within which was placed another glass beaker of 50 ml capacity in inverted position and weighted with 50 g to stop floating. The temperature system involves inserting measuring system (thermometer) in 500 ml beaker and intermittently adding hot water in outer mortar full of water. The balance was thus adjusted that right hand-side was specifically 5 g heavier than the left.

Method: The balance adjusted as explained above was further used for the study. The bovine cheek pouch, excised and washed was tied tightly with mucosal side upward using thread over the base of inverted 50 ml glass beaker. This beaker befittingly weighted was lowered into 500 ml beaker, which was then filled with isotonic phosphate buffer (pH 6.8) kept at 37^0C such that the buffer reaches the surface of mucosal membrane and keeps it dampish. This was then kept below left hand aspect of balance. The buccal tablet was then stuck to glass stopper through its backing membrane using an adhesive (Feviquick). The 5 g on right hand side is removed; this causes application of 5 g of pressure on buccal tablet superimposed dampish membrane. The balance was kept in this position for 3 min and so slowly weights were augmented on the right pan, untills tablet separates from mucosal membrane. The whole weight on right pan minus 5 g gives the force needed to separate tablet from mucosa. This gives bioadhesive strength in grams. The norm of three trials was taken for every set of formulations. when every measure, the tissue was gently and totally washed with isotonic phosphate buffer and left for five min before reading a new tablet of same formulation to get reproducible multiple results for the formulation.

Swelling Index

Swelling study was performed on 1% agar gel plates. Twenty tablets were weighed and average weight of each four tablets was calculated. The tablets were placed on the gel surface in five Petri dishes (each containing four tablets), which were placed in an incubator at 37°C. Four tablets were removed at time intervals of 1, 2, 4 and 6hrs, excess water from the surface was carefully soaked using filter paper, and swollen tablets were weighed and swelling index was calculated by using formula (Panday *et al.,* 2010).

$$Swelling\ Index = \frac{Mt - M0}{M0} \text{ X } 100 \qquad [5]$$

Where, Mt = weight of tablet at time (t) and M0= initial weight of tablet at time t = 0.

Differential Scanning Calorimetry (DSC) Study

DSC was performed in order to assess the thermotropic properties and thermal behavior of the drug and the formulation of buccal tablet. About 5 mg of sample were sealed in the aluminum pans and heated at the rate of 10^0c/min, covering a temperature range of 40^0c to 3000^0c under nitrogen atmosphere of flow rate 1000 ml/min (Shivanand *et al.,* 2010).

Powder x-ray Diffractometer Study

A powder X-ray diffractometer (Siemen's D-5000, Germany) was used for diffraction studies. PXRD studies were performed on the samples by exposing them to CuKa radiation (40 kV, 30 mA) and scanned from 2 to 70°, at a step size of 0.045 2q and step time of 0.5 s.

In-Vitro Release Study

The United state pharmacopoeia (USP) type II dissolution apparatus was used to study the release of drug from buccal tablets. The dissolution medium consisted of 500 ml of phosphate buffer pH 6.8 containing 20% methanol. Study was performed at 37 ± 0.5°C, at a rotation speed of 50 rpm. Samples (5 mL, at each time) were withdrawn at pre-determined time intervals and replaced with fresh medium. The samples were filtered through whatman filter paper no. 41 with appropriate dilutions with phosphate buffer pH 6.8 and were assayed spectrophotometrically at 241 nm against phosphate buffer pH 6.8 as blank. Kinetics of dissolution was studied by fitting the in vitro release data into following mathematical equations (Ankarao *et al.,* 2010; Ganesh and Pallaprola 2011),

Zero Order Kinetics: A zero-order release would be predicted by the following equation:

$A_t = A_0 - K_0t$ [6]

Where, A_t = Drug release at time t**,** A_0 = Initial drug concentration, K_0 = Zero-order rate constant

First Order Kinetics: A first-order release would be predicted by the following equation:

$$\text{Log } C = \text{Log } C_0 - \frac{K_t}{2.303} \qquad [7]$$

Where, C = Amount of drug remained at time 't'; C_0 = Initial amount of drug and K = First-order rate constant

Higuchi's Model: Drug released from the matrix devices by diffusion has been described by following Higuchi's classical diffusion equation:

$$Q = \left[\frac{D\varepsilon}{\tau}(2A - \varepsilon C_S)C_S t\right]^{½} \qquad [8]$$

Where, Q = Amount of drug released at time t, Q = Amount of drug released at time t, D = Diffusion coefficient of the drug in the matrix, A =Total amount of drug in unit volume of matrix, Cs = The solubility of the drug in the diffusion medium, ε = Porosity of the matrix, τ = Tortuosity and t = Time (hrs) at which 'Q' amount of drug is released.

Korsmeyer and Peppas Model: The release rates from controlled release polymeric matrices can be described by the following equation.

$$Q = K_1 t^n \qquad [9]$$

Q is the percentage of drug released at time t, K is a kinetic constant incorporating structural and geometric characteristics of the tablets and 'n' is the diffusional exponent.

RESULTS AND DISCUSSION

Preformulation Studies of Physical Mixture

Compatibility Studies

Fourier Transform Infrared (FTIR) Analysis

IR spectra of carvedilol showed some characteristic peaks related to C-H stretching, C-O-R stretching, C=O stretching, C=C stretching and C-N stretching at 2939 cm^1, 1786.88 cm^1, 1681.62 cm^1, 1538.11 cm^1 and 1211.26 cm^1. Similar peaks with some shifting were observed in IR spectra of optimized formulation conforms that there were no chemical interactions between all components of the system but only physical interactions was there. IR spectra of carvedilol and optimized batch are shown in Figure 1.

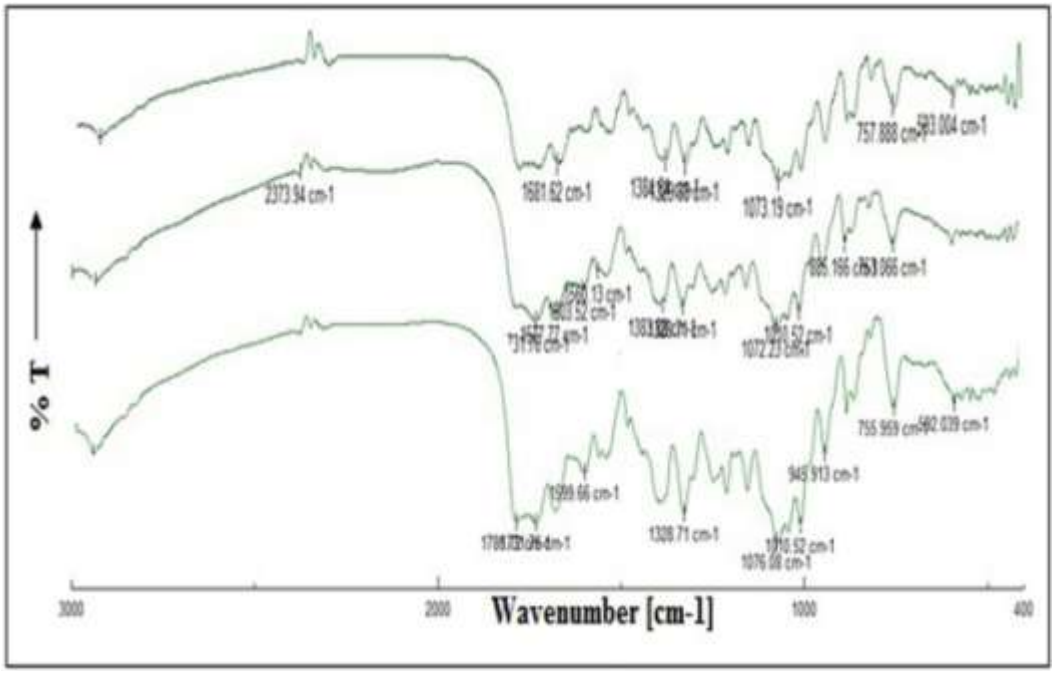

Figure 1: FTIR spectra of a) pure carvedilol b) Physical mixture of carvedilol and Guar gum c) carvedilol and Xanthan gum d) carvedilol and Sodium alginate

Flow Properties

Angle of Repose

Angle of repose for blend of all batches (F1-F8) was found to be in the range of 16.69±0.081to 22.45±0.067 which is indicative of excellent flow properties. Angle of repose was found to be maximum for the batch F3 and minimum for batch F5 (Table 2).

Table 2: Flowability parameters of physical mixture of carvedilol bilayer buccal tablet

Formulation Code	Angle of Repose (°)	Bulk Density (g/ml)	Tapped Density (g/ml)	Carr's index (%)	Hausner's ratio
F1	17.08±0.029	0.427±0.049	0.492±0.016	13.21±0.024	1.15±0.026
F2	17.92±0.059	0.481±0.086	0.566±0.036	15.72±0.055	1.17±0.048
F3	22.45±0.067	0.406±0.084	0.467±0.045	13.06±0.046	1.15±0.047
F4	18.26±0.043	0.467±0.051	0.549±0.017	14.93±0.015	1.17±0.026
F5	16.69±0.081	0.416±0.058	0.503±0.074	17.29±0.047	1.20±0.076
F6	18.26±0.087	0.419±0.049	0.496±0.042	15.52±0.069	1.18±0.087
F7	19.48±0.046	0.526±0.085	0.586±0.064	10.23±0.025	1.11±0.046
F8	21.55±0.048	0.483±0.023	0.542±0.046	10.88±0.087	1.12±0.016

**All value are expressed as mean ± SD (n=3)*

Carr's Compressibility Index (CCI) and Hausner's Ratio (HR)

Carr's compressibility index for blend of all batches (F1-F8) was found to be in the range of 10.23±0.025 to 17.29±0.047 which indicates good flow properties. Carr's compressibility index was found to be maximum for the batch F5 and minimum for batch F7.

Hausner's ratio was found to be in the range of 1.11±0.046 to 1.20±0.076 which indicates good flowability. Hausner's ratio was found to be maximum for the batch F5 and minimum for batch F7. Results of all parameters of flow properties are shown in Table 2.

Evaluation of Mucoadhesive Bilayer Buccal Tablet of Carvedilol

Hardness, Thickness and Friability

The results of evaluation of mucoadhesive bilayer buccal tablet of carvedilol are given in Table 3. The tablets were found uniform with respect to thickness (2.36 to 2.86mm). Hardness (4.3 to 5.1 kg/cm^2) and friability (0.31 to 0.51%) were also found uniform indicating good handling property of the prepared bilayer matrix tablets (Table 3).

Weight Variation and Drug Content

It was observed that all tablets from each batch were within the specified limits, hence passes the tests as per IP. The % drug content of all formulation was found to be in the range of 97.26 to 102.02% (Table 3).

Table 3: Evaluation of mucoadhesive bilayer buccal tablet of carvedilol

Formulation Code	Hardness (kg/cm^2)	Thickness (mm)	Friability (%)	Weight variation (mg)	Drug content
F1	4.5±0.251	2.43±0.152	0.51±0.021	147.21±0.49	101.58±1.19
F2	5.1±0.2	2.83±0.057	0.42±0.043	151.29±0.26	97.26±2.03
F3	4.3±0.321	2.36±0.251	0.49±0.011	148.64±0.13	101.08±1.89
F4	4.7±0.416	2.86±0.251	0.37±0.025	149.86±0.72	99.41±1.47
F5	4.3±0.208	2.26±0.152	0.42±0.036	150.46±0.03	97.56±2.06
F6	4.7±0.556	2.7±0.254	0.48±0.016	149.32±0.36	97.26±1.24
F7	4.4±0.435	2.5±0.264	0.38±0.026	150.19±0.09	102.02±2.16
F8	4.7±0.602	2.36±0.251	0.31±0.031	151.43±0.29	98.69±0.73

**All value are expressed as mean ± SD (n=3)*

Surface pH

The observed pH of the different batches of tablets (F1-F8) is shown in Table 4. Study reveals that all formulations provide an acceptable pH range of 6.13 to 6.63. Hence may not produce any local irritation to the mucosa.

Ex vivo Mucoadhesive Strength

The mucoadhesive strength observed for the different tablets is shown in Table 4. The mucoadhesion of all the buccal tablets of varying ratios of polymers were tested and weight required to pull off the formulation from the mucous tissue is recorded as mucoadhesion strength in grams. The mucoadhesive strength of buccal tablets was found to be highest in case of batch F4 (14.09 gm). This may be due to fact that positive charges on surface of carbopol could give rise to strong electrostatic interaction with mucous or negatively charged mucus membrane. While, poor mucoadhesive strength was observed in case batch F5.

Table 4: Surface pH and Mucoadhesive strength of mucoadhesive bilayer buccal tablet of carvedilol

Formulation batch	Surface pH	Mucoadhesive strength (gm)
F1	6.63±0.305	9.68±0.46
F2	6.26±0.568	11.38±0.29
F3	6.46±0.378	13.57±0.19
F4	6.43±0.351	14.09±0.21
F5	6.13±0.305	7.56±0.47
F6	6.16±0.808	10.15±0.06
F7	6.36±0.832	10.95±0.84
F8	6.5±0.3	12.48±0.25

**All value are expressed as mean ± SD (n=3)*

Swelling Index

Swelling index or water uptake test is of great significance, as variation in the water content causes significant variation in the mechanical properties of the formulation.

Table 5: Swelling study of mucoadhesive bilayer buccal tablet of carvedilol

Time (hrs)	F1	F2	F3	F4	F5	F6	F7	F8
1	31.16±0.10	29.54±187	25.03±1.54	23.14±0.89	33.98±1.26	30.06±1.26	27.45±0.69	23.89±1.26
2	39.26±0.90	35.96±1.69	28.47±1.06	27.69±1.98	37.26±1.94	35.08±0.98	31.57±1.21	29.87±0.32
3	44.09±1.12	41.03±1.48	34.16±0.85	32.54±1.06	45.69±0.65	43.85±1.09	36.47±1.06	33.56±1.05
4	51.85±1.06	49.26±1.85	39.58±1.36	37.24±0.94	55.29±1.98	50.67±1.68	43.69±1.54	39.76±1.84
5	57.26±1.57	53.78±1.63	42.73±0.58	40.26±1.56	62.04±0.64	59.04±1.40	49.81±1.36	41.09±1.06
6	62.75±1.43	60.09±0.96	50.02±1.43	45.95±1.59	68.46±1.74	64.29±0.98	54.57±0.98	49.38±1.54
7	72.65±0.96	65.48±1.23	52.34±0.87	48.57±1.94	71.06±1.61	67.39±1.68	58.35±1.03	53.76±0.36
8	76.59±1.09	68.26±1.21	59.06±1.14	51.41±1.84	73.56±0.22	71.05±1.05	62.06±0.75	57.89±1.13

**All value are expressed as mean ± SD (n=3)*

Table 5 depicts the swelling behavior of different matrix tablet. Tablet containing guar gum have higher swelling index as compare to tablet containing xanthan gum. It was found that increase in the concentration of both guar gum and xanthan gum reduced the swelling index. In case batches containing guar gum (F1-F4) and xanthan gum (F5-F8) swelling index were found to be higher in batch F1 and F5. Noteworthy, although batch F1, F2 and batch F5, F6 contains same amount of guar gum (20 mg) and

xanthan gum (20 mg) it is interesting to see that there is difference in swelling index. This difference in swelling index may be attributed to the presence of sodium alginate in batch F2 and F6 (Table 5).

Differential Scanning Calorimetry (DSC) Study

DSC thermogram of carvedilol showed a sharp endothermic peak at 115°C corresponding to its melting point. While DSC thermogram of carvedilol bilayer tablet formulation showed absence of sharp peak and peak also shifted towards the lower value. This absence of sharp peak may be attributed to amorphous nature of formulation and uniform distribution of drug. DSC thermogram of pure carvedilol and formulation are shown in Figure 2.

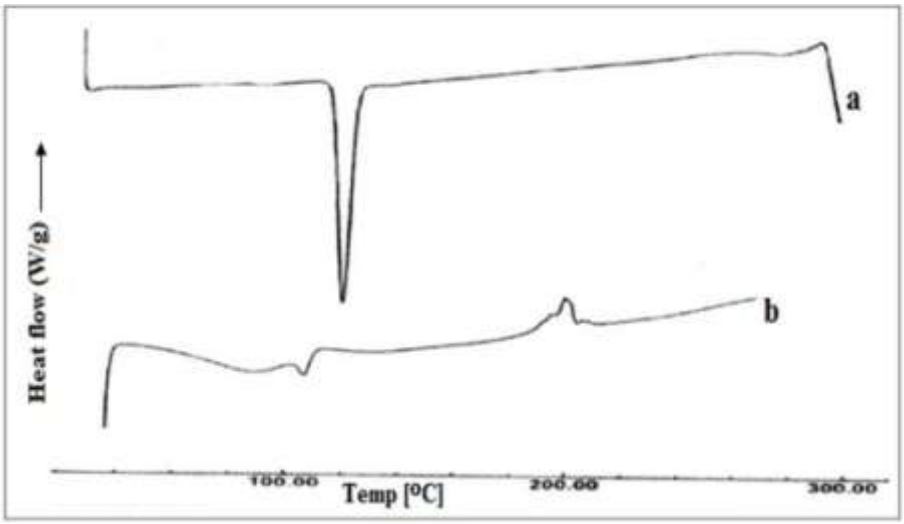

Figure 2: DSC spectra of a) carvedilol and b) optimized formulation of carvedilol bilayer buccal tablet

Powder x-ray Diffractometer Study

PXRD spectra of pure carvedilol showed higher intensity peak nearly at 17°, 19°, 21° which clearly indicates the crystalline nature of carvedilol. Noteworthy PXRD spectra of formulation showed peak retained at the same position with higher intensity (Figure 3).

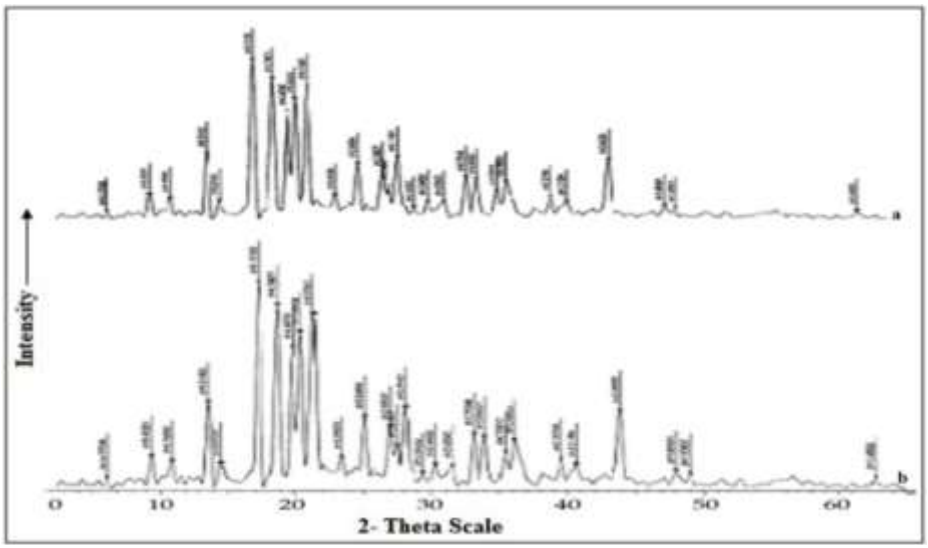

Figure 3: PXRD spectra of a) carvedilol and b) optimized formulation of carvedilol bilayer buccal tablet

In Vitro Drug Release Studies

In vitro drug release studies were carried out in USP XXIII tablet dissolution test apparatus-II employing paddle stirrer at 50 rpm and 200 ml of pH 6.8 phosphate buffer as dissolution medium. The *in vitro* dissolution data of all the designed batches (F1-F8) are shown in Tables 6, and plot of % cumulative drug release vs time is depicted in Figures 4. From dissolution data it is evident that designed all formulations (Batch F1-F8) have displayed more than 77% of drug release at the end of 8 h. Kinetics of dissolution were studied by subjecting the *In vitro* drug release data of all the buccal tablet formulations of carvedilol to linear regression analysis according to zero order, first order kinetics and according to Higuchi's and Peppas equations. The results of linear regression analysis including regression coefficients are summarized in Table 7. Study reveals that all the formulations followed zero-order release kinetics ('r' values from 0.9608 to 0.9951). Higuchi and Peppas data showed that the drug is released by non-Fickian diffusion mechanism ('r' values from 0.9821 to 0.9996 and 'n' values from 0.682 to 0.821).

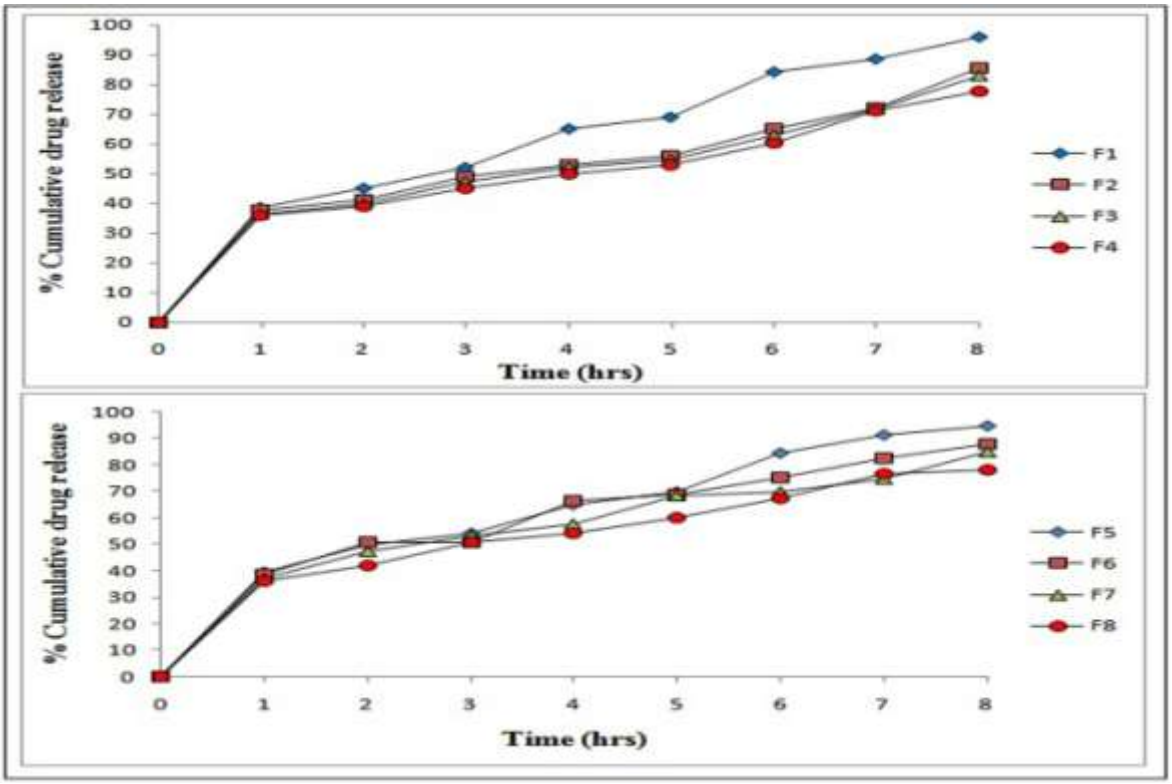

Figure 4: Comparative dissolution profile of carvedilol bilayer buccal tablet formulated with a) guar gum b) Xanthan gum

Table 6: Dissolution data of carvedilol mucoadhesive bilayer buccal tablet

Time (hr)	F1	F2	F3	F4	F5	F6	F7	F8
0	00	00	00	00	00	00	00	00
1	38.64	37.61	36.24	35.89	39.67	38.81	37.27	36.06
2	45.00	41.04	40.01	38.98	49.63	50.83	47.57	41.99
3	51.87	48.77	47.40	44.82	54.27	51.02	53.41	51.01
4	64.92	53.07	52.04	49.63	64.92	66.46	57.70	54.27
5	69.04	55.99	54.79	52.72	69.73	68.87	68.35	60.28
6	84.04	64.88	63.03	60.28	84.50	75.40	69.73	67.67
7	88.62	72.13	71.45	70.93	91.20	82.78	74.88	76.94
8	96.01	85.36	82.78	77.46	94.80	87.76	84.84	78.32

Table 7: Drug release kinetics of the formulated product of carvedilol

Formulation code	Zero order R^2	First order R^2	Highuchi R^2	Korsmeyer –Peppas N	R^2
F1	0.9809	0.8926	0.9492	0.7468	0.9916
F2	0.9929	0.9436	0.9638	0.6904	0.9936
F3	0.9913	0.9048	0.9681	0.6345	0.9952
F4	0.9986	0.8614	0.9675	0.6847	0.9984
F5	0.9891	0.8129	0.9689	0.6485	0.9968
F6	0.9903	0.8726	0.9685	0.7345	0.9976
F7	0.9926	0.8669	0.9847	0.6581	0.9958
F8	0.9961	0.9189	0.9658	0.6948	0.9968

Conclusion

The prepared mucoadhesive bilayer buccal tablets of carvedilol can avoid the first pass metabolism of carvedilol and can improve the systemic bioavailability of carvedilol. As the surface pH of the all formulation were close to neutral pH so there are minimal chances of buccal cavity irritation. Batch F4 showed drug release retardation (77.46%) at the end of 8 hr and showed higher mucoadhesive strength (14.09±0.21). Noteworthy, as the amount of polymer (Xanthan gum and Guar gum) in the tablets increases, the drug release rate and swelling index decreases, whereas mucoadhesion strength increases. So eventually it can be concluded that guar gum along with Na-alginate can be more useful in drug retardation and for higher mucoadhesive strength as compare to xanthan gum and Na-alginate combination.

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