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Formulation & Effect of Polymers on Mucoadhesive Buccal Patch of Carvedilol Using Factorial Design

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ABSTRACT

The study aim was concerned with formulation and in vitro evaluation of mucoadhesive buccal patch of carvedilol, which is extensively metabolized by liver. During last few years mucoadhesive dosage forms have promoted an area of drug delivery system that renders the treatment more effective and safe, not only for topical disorders but also for systemic problems. Therefore the present investigation is concerned with the development of the bucco-mucoadhesive patches, which were designed to prolong the buccal residence time, to increase penetration through buccal mucosa and thus increase the bioavailability. Various formulations were developed by using release rate controlling patches forming polymers like HPMC (K15, K4), HPC-L, Sodium alginate, PVP K30& Carbopol 934P in alone & various combinations by solvent casting technique using plasticizer glycerol. For unidirectional release, backing layer prepared using ethyl cellulose 2.5%w/v dissolve in isopropyl alcohol and acetone. Glycerol used as a plasticizer was casted on the patches. The patches were evaluated for their thickness uniformity, folding endurance, weight uniformity, content uniformity, swelling behaviour, tensile strength, and surface pH, *In vitro* release studies, in vitro residence time, in vitro diffusion study. Patches exhibited drug release (diffusion) in the range of 75.69% to 96.53%. Kinetic models i.e. Higuchi, Korsemeyer-peppas, zero order were applied on data of diffusion release to explain release. The optimized formulation (F1) shows the zero order release.

Keyword: Buccal Patch, Carvedilol, Bioadhesion, Mucoadhesion, Buccal Drug Delivery.

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INTRODUCTION

The buccal site differs from the sublingual in following respects. The buccal mucosa is less permeable than the sublingual and does not give the rapid onset of absorption seen with sublingual delivery. The buccal mucosa appears to be better suited to the use of retentive systems, such as a mucoadhesive tablets, patches, disks, strips, ointments and gels. The oral mucosal drug delivery systems can be localized easily and well accepted by patients[1] The total surface of the oral cavity is about 100 cm^2 The mucosal membranes of the oral cavity can be divided into five regions such as the floor of the mouth (sublingual), the buccal mucosa (cheeks), the gums (gingival), palatal mucosa, and the lining of the lips. These oral mucosal regions are different from each other in terms of anatomy, permeability to drug, and their ability to retain a system for a desired length of time. Although the buccal mucosa is less permeable than the sublingual mucosa and it does not yield a rapid onset of action as seen with sublingual delivery, mucosa of the buccal area has an expanse of smooth and relatively immobile surface, which is suitable for placement of retentive system. These characteristics make the buccal mucosa a more appropriate site for prolonged systemic delivery of drugs[3]. Buccal patches are more advantageous because they can be readily attached to the buccal cavity and are easily removed and thus, they are more highly flexible.

- Much more readily tolerated by the patients than tablets and gels.
- Patches also ensure more accurate dosing of the drug compared to gels and ointments[4,5,6,7]

These attributes make buccal mucosa more suitable for controlled delivery applications. In addition, there is excellent acceptability and the drug can be applied localized, and may be removed easily at any time during the treatment period. A few drugs such as Metoprolol Tartarate, Ibuprofen, Sulbotamol Sulphate, Diltaizem Hydrochloride, Isosorbide Dinitrate have been successfully administered via the buccal route[8] Carvedilol is a non- selective β-adrenergic blocking agent with α1-blocking activity. It is widely used to treat essential hypertension and angina pectoris. Though it is rapidly absorbed after oral administration, the bioavailability of carvedilol is 25-35%[9], as it undergoes stereo-selective first pass metabolism and will be eliminated from body through urine (16%) and feces (60%). Carvedilol is a weak base and its p*Ka* value is approximately 7.8, which satisfies the criterion for the selection of the drug. The log PC (partition coefficient) value for carvedilol is about 3.967. It indicates that carvedilol has sufficient lipophilicity to pass through the buccal membranes. The t_{max} of carvedilol is 1.2h[10] by

per oral route, which is long and variable. The dose of carvedilol is 25 mg twice a day, however, a lower effective dose is reported to be approximately 3.125 mg[11]. By observing the above points, it is inferred that carvedilol has a need to formulate into buccal patches and the drug is suitable for it[12].

The purpose of this study was to develop formulations and systematically evaluate in vitro performances of buccoadhesive patches of carvedilol using the different polymers in alone and in combination to modify the rate of drug release. A 3^2 full factorial design was employed to study the effect of the independent variables HPMC K4 and HPC-L in different ratios on dependent variables like swelling index, t50%, ex vivo mucoadhesive strength, and ex vivo residence time.

MATERIAL AND METHODS

Material

Carvedilol was gifts from Amneal pharmaceutics co (I) Ltd. Ahmadabad. All other reagents and chemicals used were of analytical reagent grade from the college sources.

Preparation of Mucoadhesive Buccal Patches[13]

Preliminary screening

Mucoadhesive buccal patches of carvedilol were prepared by solvent casting method using different mucoadhesive polymers such as HPMC (K4M, K4M) HPC-L, Sodium alginate, Carbopol, and Ethyl Cellulose (20 cps). Total polymers concentrations were used 2% w/v. The water was used as casting solvent for patches containing HPMC (K4M, K4M), HPC-L, Sodium alginate, Carbopol. Methanol was used for solubilising drug (carvedilol), glycerol was used as plasticizers. Acetone and isopropyl alcohol was used as solvent in ratio of 3:2 for ethyl cellulose backing membrane. Initially drug free patches were prepared by using these polymers alone and in combination. Glycerol was used as plasticizers with concentration 15% w/w based on total polymers weights. The detail composition of polymers, solvent systems and plasticizer are shown in table 1

Table 1 Preliminary work

Ingredients	A1	A2	A3	A4	A5	A6	A7	A8	A9	A10
Carvedilol	175.6	175.6	175.6	175.6	175.6	175.6	175.6	175.6	175.6	175.6
HPMCK4M	600	-	-	-	400	300	200	-	-	-
HPMCK15M	-	600	-	-	-	-	-	400	300	200
HPC –L	-	-	600	-	200	300	400	200	300	400
Sodium alginate	-	-	-	*600*	-	-	-	-	-	-
Glycerol (%)	15	15	15	*15*	15	15	15	15	15	15
Methanol (ml)	5	5	5	*5*	5	5	5	5	5	5

Preparation of Drug Free Patches

The drug free patches were prepared by casting solvent technique. The polymers (2% w/v) were dissolved in casting solvent and plasticizer(s) (15% w/w of polymers) was incorporated. The polymers solution was mixed thoroughly with the help of magnetic stirrer till homogenous mixture was formed then polymeric solution (30 ml) was poured within a glass bangle (9.2 cm diameter) placed on a mercury substrate in a petridish and allow to dry in oven for 12 hrs at 60^0C. For evaporating solvent, the rate of evaporation was controlled by inverting the cut funnel over the petridish. The dried patches were cut into 2.0 cm diameter packed in aluminium foil and stored in desiccators until further use.

Preparation of buccal patch of carvedilol

The polymers (2% w/v) were dissolved in casting solvent (20ml) and plasticizer(s) (15% w/w of polymers) were incorporated then calculated amount of drug dissolved in methanol (5ml) was added in polymeric solution with continuous stirring till homogeneous mixture was formed. This 30 ml of the solution was poured within glass bangles (7.5 cm diameter) which was placed on a mercury substrate in a petridish and allow drying for 12 hrs at 60°c in oven till flexible patches was formed. For evaporating solvent the rate of evaporation was controlled by inverting the cut funnel over the petridish.

Preparation of backing layer:

The dried patches were removed and stick the backing membrane of ethyl cellulose to one side of the buccal patch with UcecrylTM. The backing membrane of ethyl cellulose was prepared by dissolving in acetone and isopropyl alcohol. Then place for evaporation. The dried patches were removed and stick the backing membrane of ethyl cellulose to one side of the buccal patch with UcecrylTM. Then these composite patches were cut into 2.0 cm diameter and wrapped in aluminium foil and stored over fused calcium chloride in desiccators at room temperature until further use.

Physicochemical evaluation of carvedilol buccal patches:

Thickness uniformity of the patches[14]

The thickness of each patch was measured using screw gauge at five different positions of the patch and the average of was calculated.

Folding Endurance[15]

Three patches of each formulation of size (2x2 cm) were cut by using sharp blade. Folding endurance was determined by repeatedly folding a small strip of patch at the same place till it

broke. The number of times, the patch could be folded at the same place without breaking gave the value of folding endurance. The mean value was calculated.

Drug Content Uniformity[16]

A 2 cm2 patches was cut into small pieces, dissolved into 10 ml of methanol and diluted upto 100 ml with the phosphate buffer (pH 6.8), and shaken continuously. Then filtered the solution, the drug was estimated spectrophotometrically at 275 nm after dilution.

Swelling Study[17]

Ratios of the polymeric patches were determined by placing the polymeric patches in 5 ml of distilled water. The swelling ratio was measured as a function of time at room temperature. At predetermined time intervals, residual water was removed and the weight of the swelled patches was measured. The swelling ratio was calculated by using [(Wp - Ws)/Ws] x 100, where Ws and Wp are the weight of the dry patches before testing and the weight of swelled patches after testing, respectively.

***In-vitro* diffusion studies**[18]

The *in-vitro* buccal drug permeation study of carvedilol through the sheep buccal mucosa was performed using Franz diffusion cell at 37 ± 0.2°C. Fresh sheep buccal mucosa was mounted between the donor and receptor compartments. The buccal tablet was placed with the core facing the mucosa and both compartments were clamped together. The donor compartment was filled with 1 ml of phosphate buffer pH 6.8. The receptor compartment (55 ml capacity) was filled with isotonic phosphate buffer pH 7.4 and the hydrodynamics in the receptor compartment was maintained by stirring with a magnetic bead at 50 rpm. 1 ml samples were withdrawn at predetermined time intervals and after appropriate dilution with isotonic phosphate buffer pH 7.4, analyzed at 240.5 nm using a UV spectrophotometer.

Measurement of Mechanical Properties[19]

Mechanical properties of the patche (patches) were evaluated using a microprocessor based advanced force gauze equipped with a motorized test stand (Ultra Test, Mecmesin, West Sussex, UK), equipped with a 25 kg load cell. Patches strip with the dimensions 60 x 10 mm and without any visual defects were cut and positioned between two clams separated by a distance of 3 cm. Clamps were designed to secure the patch without crushing it during the test, the lower clamp was held stationary and the strips were pulled apart by the upper clamp moving at a rate of 2 mm/sec until the strip broke. The force and elongation of the patches at the point when the strip broke was recorded. The tensile strength and elongation at break values were calculated using the formula.

$$\text{Tensile strength (kg.mm-2)} = \frac{\text{Force at break (kg)}}{\text{Initial cross sectional area of the sample (mm2)}}$$

$$\text{Elongation at break (\%.mm-2)} = \frac{\text{Increase in length (mm)}}{\text{Original length}} \times \frac{100}{\text{Cross sectional area (mm2)}}$$

Surface pH[20]

Patches were left to swell for 1 h on the surface of agar plate, prepared by dissolving 2% (m/V) agar in warmed phosphate buffer of pH 6.8 under stirring and then set aside till gelling at room temperature. The surface pH was measured by means of a pH paper placed on the surface of the swollen patch. The mean of three reading was recorded.

***In-vitro* Release Studies of Carvedilol from Buccal Patches**[21]

The drug release was determined using U.S.P. dissolution test apparatus (paddle over disk type) thermo stated at 37 ±10 C and stirred at a rate of 50 rpm. Sink condition was maintained throughout the study. Each patch was fixed on glass slide with the help of Cyanoacrylate adhesive, so that the drug could be released only from upper face. The slide was immersed in the vessel containing 250 ml of phosphate buffer pH 6.8. Aliquots of 5 ml of sample were withdrawn with graduated pipette at every one hour time intervals up to 12 hours with equal volume of phosphate buffer[22,23] The sample were diluted with phosphate buffer and analyzed spectrophotometrically at 240nm and the cumulative amount of drug released at various time intervals was calculated. The test was carried out in triplicates.

Ex Vivo Mucoadhesive Strength[24,25]

Bioadhesive strength of the patch was measured on a modified physical balance. The fresh sheep buccal mucosa was cut in to pieces and washed with phosphate buffer pH 6.8. A piece of buccal mucosa was tied to the open mouth of a glass vial, which was filled completely with phosphate buffer pH 6.8. The glass vial was placed and tightly fitted in the centre of glass beaker. The phosphate buffer (pH 6.8, 37 ± 10^0C) was filled in the glass beaker just touches the mucosal surface. The patch was stuck to the lower side of rubber stopper with Cyanoacrylate adhesive. Two pans of the balance were balanced with 5 gm weight on the right hand side pan. A weight of 5 gm was removed from the right hand side pan, which lowered the pan along with the patch over the mucosa. The balance was kept in this position for 5 min. contact time. The water (equivalent to weight) was added slowly with infusion set (100 drops/min.) to the right-hand side pan until the patch detached from the mucosal surface. The weight in grams required to detach the patch from the mucosal surfaces gave the measure of mucoadhesive strength.

Ex Vivo Residence Time[26]

The ex vivo mucoadhesion time was studied (n = 3) after application of patches on freshly cut sheep buccal mucosa.22 The fresh sheep buccal mucosa was fixed in the inner side of a beaker, about 2.5 cm from the bottom, with Cyanoacrylate glue. One side of each patch was wetted with 1 drop of phosphate buffer (pH 6.8) and pasted to the sheep buccal mucosa by applying a light force with a fingertip for 30 seconds. The beaker was filled with 200 mL of phosphate buffer (pH 6.8) and was kept at 37-C ± 1-C. After 2 minutes, a 50-rpm stirring rate was applied to simulate the buccal cavity environment, and patch adhesion was monitored for 12 hours. The time required for the patch to detach from the sheep buccal mucosa was recorded as the mucoadhesion time.

Stastical analysis

3^2 Full Factorial Designs

A 3^2 randomized full factorial design was employed in the present study. In this design 2 factors were evaluated, each at 3 levels, and experimental trials were performed for all 9 possible combinations. The polymer HPMC K4M consider as (X_1) and HPC-L consider as copolymer (X_2) were chosen as independent variables in 3^2 full factorial design, t50, in vitro diffusion release, mucoadhesive strength, and swelling index were taken as dependent variables. The prepared formulations were evaluated for drug content uniformity, swelling index, ex vivo mucoadhesive strength, in vitro dissolution study, in vitro diffusion study, thickness, tensile strength, elongation at break etc(Table 2).

Table 2 Coding of variable

Coded Values	Actual Values	
	***X_1* = Polymer (HPMC K4M)**	***X_2* = Copolymer (HPC-L)**
-1	350	150
0	400	200
1	450	250

A statistical model incorporating interactive and poly nominal terms was used to evaluate the responses.

$$Y = b_0 + b_1X_1 + b_2X_2 + b_{12}X_1X_2 + b_{11}X_1^2 + b_{22}X_2^2$$

Where Y is the dependent variable, b_0 is the arithmetic mean response of the 9 runs, and b_1 is the estimated coefficient for the factor Xi. The main effects (X_1 and X_2) represent the average result of changing 1 factor at a time from its low to high values. The interaction terms (X_1X_2) show how the response changes when two factors are simultaneously changed. The polynomial terms

(X_1^2 and X_2^2) are included to investigate nonlinearity. The polynomial equations can be used to draw conclusions after considering the magnitude of coefficient and the mathematical sign it carries (i.e., negative or positive).

R^2 value for t50, in vitro diffusion release, swelling index, mucoadhesive strength, diffusion coefficient (n), and release rate constant (K) are 0.9849, 0.9949, 0.9804, 0.9867, 0.8495 and 0.9745 respectively indicating good correlation between dependent and independent variables. The reduced models were developed for response variables by omitting the insignificant terms with $P>0.05$. The terms with $P<0.05$ were considered statistically significance and retained in the reduced model.

Analysis of release mechanism

The kinetic model were used a zero order equation, first order equation, higuchi release, Korsemeyer and peppas models.

RESULT & DISSCUSION

The preliminary batches of carvedilol were evaluated for important parameters like swelling index, ex vivo mucoadhesive strength, in vitro drug release, *in vitro* residence time and general appearance. In preliminary trial, dummy Patches containing carbopole 934P, and PVP K30 were not satisfactory in appearance. In preliminary batch, A3 & A7 showed the lowest ex vivo mucoadhesive strength on sheep buccal mucosa, which indicated that HPC-L have less mucoadhesive properties (Table 3).

Table 3 Evaluation parameter of preliminary batches

Batch code	Tensile strength ($kg.mm^{-2}$)	Elongation at break (%)	Swelling index (%)	Mucoadhesive strength (gm)	Diffusion data	In vitro residence time (min)	Folding endurance
A1	6.7	24.59	39.13	18	60.91	506	>300
A2	7.8	28.85	47	26	51.44	535	>300
A3	5.5	20.18	24	16	64.10	200	>300
A4	9.8	32.46	28	20	44.41	485	>300
A5	6.5	22.54	35.61	23	84.41	494	>300
A6	6	20.88	30	21	58.64	380	>300
A7	5.9	20	29	15	69.18	279	>300
A8	7.1	24.15	44	28	52.78	516	>300
A9	6.6	22.06	36	24	45.97	400	>300
A10	6.08	21.13	31	22	49.69	321	>300

Patches did not show any cracks even after folding for more than 300 times. Hence it was taken as the end point. Folding endurance did not vary when the comparison was made between

dummy patches and drug-loaded patches. The swelling of the patches were observed in phosphate buffer solution (pH 6.8) and data are shown in Table 2. Swelling was more pronounced in patches A1 which contains more HPMCK15 than the other, Patches A3 showed least swelling which contains HPC-L. The order of patches for their swelling properties is A2>A8>A1>A9>A5>A10>A6>A7>A4>A3.

The hydrophilic polymer HPMCK15M significantly improved the bioadhesion of patches but decreased the drug release because of high swelling index, as shown in A2, A8, A9 & A10. Also, incorporation of the hydrophilic polymer HPC-L enhanced the drug release but significantly decreased the mucoadhesive strength. Patches containing drug and sodium alginate had an unsatisfactory physical appearance. Patches containing a higher concentration of HPC-L had an unsatisfactory physical parameter (A6, A7, A9, & A10), while patches containing a low concentration of HPC-L had a good physical appearance and satisfactory evaluation parameter. On the basis of preliminary trials, it was concluded that, the combination of HPMC K4M & HPC (formulation A5) gave better drug release from the FTIR spectra it was conclude that that was no interaction between drug and polymer (Figure 1 & 2) and mucoadhesive strength than the other batches, also should be satisfactory. After that buccoadhesive patches of Carvedilol using formulation A5 were prepared by full factorial design to obtain good physical properties as shown in Table 4.

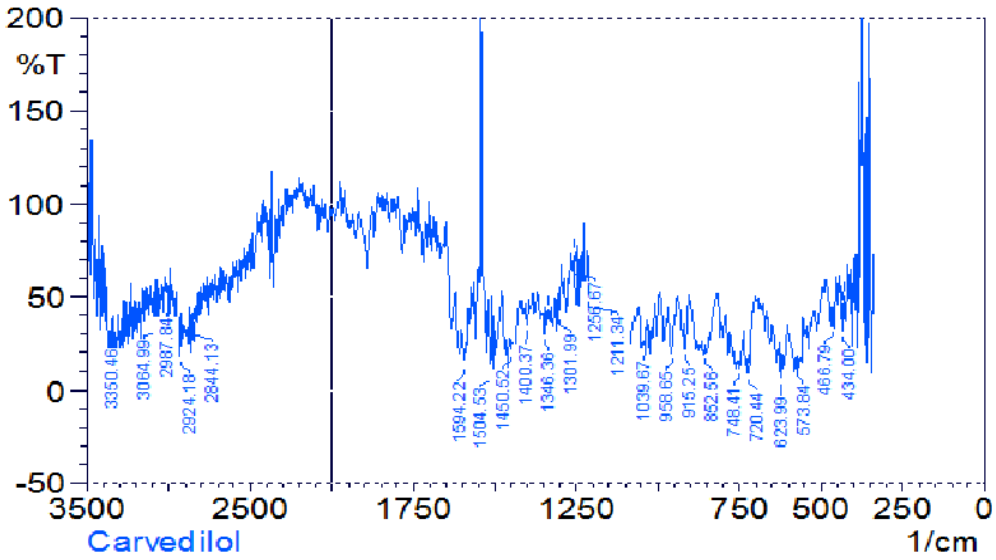


Figure 1 FTIR Spectroscopy of Drug

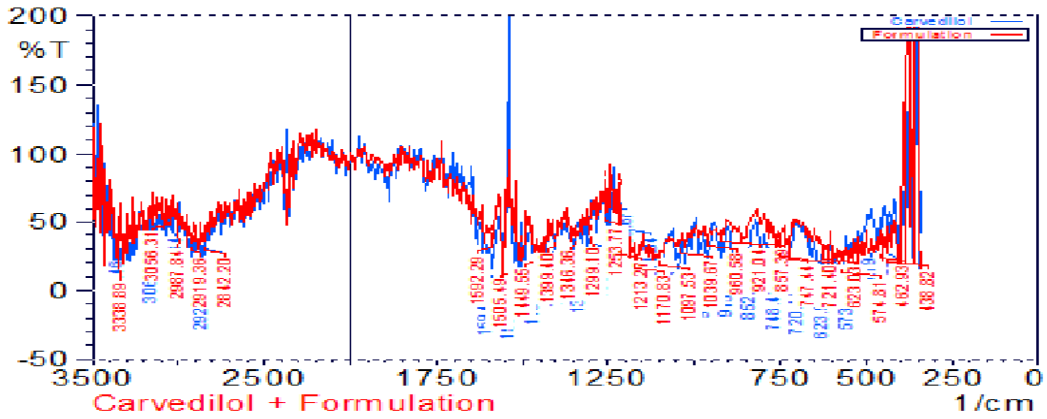


Figure 2 FTIR Spectroscopy of Drug & Formulation

Table 4 Final Factorial Batch of Carvedilol Buccal Patch

Formulation Ingredients	Batch Code								
	F1	F2	F3	F4	F5	F6	F7	F8	F9
Carvedilol	6.25	6.25	6.25	6.25	6.25	6.25	6.25	6.25	6.25
HPMC K4M(mg)	350	350	350	400	400	400	450	450	450
HPC(mg)	150	200	250	150	200	250	150	200	250
Glycerol (%)	15	15	15	15	15	15	15	15	15
Methanol (ml)	5	5	5	5	5	5	5	5	5
Water (ml)	20	20	20	20	20	20	20	20	20

Evaluation Parameters of factorial batches F1-F9

In factorial batch in vitro diffusion study, t50, swelling index and ex vivo mucoadhesive strength were consider as dependent variable which shown in table. All the evaluation parameter of factorial batch is given table 5.

Thickness uniformity

All the patches have uniform thickness throughout. Average thickness was found to be in the range of 0.11 to 0.30mm as shown in table 5. As the polymeric content increases, the thickness of the patch also increases.

Folding endurance

Films did not show any cracks even after folding for more than 300 times shown in table 5. Hence it was taken as the end point. Folding endurance did not vary when the comparison was made between plain films and drug loaded films.

Weight uniformity

The patches were found uniform. The average weight of the patch found was found to be in the range of 42.66 to 62.5 mg shown in table 5. as the polymer content increase, the weight of the patch also increased.

Table 5 Results of Evaluation Parameters for buccal patch of Batches F1-F9

Parameter	Batch code								
	F1	**F2**	**F3**	**F4**	**F5**	**F6**	**F7**	**F8**	**F9**
Ex vivo residence time (min)	478	481	483	490	492	495	500	510	518
Thickness (m±S.d)	0.11±0.01	0.14±0.06	0.27±0.03	0.25±0.09	0.23±0.02	0.29±0.04	0.29±0.03	0.29±0.01	0.30±0.04
Folding Endurance	>300	>300	>300	>300	>300	>300	>300	>300	>300
Drug Content (m±s.d)	101.29±0.5	98.35±0.58	97.37±0.62	99.71±0.07	97.95±0.08	90.13±0.56	99.90±0.75	96.13±0.05	98.54±0.38
Weight Uniformity (m±s.d)	42.7±3.06	44.1±9.89	46.1±12.1	47.1±4.05	48.4±6.5	50.2±8.5	54.8±1.9	56.3±3.05	62.5±1.68
Tensile Strength (m±s.d)	5.3±0.9	5.6±0.08	6±0.035	6.4±0.05	6.4±0.05	6.7±0.12	6.9±0.07	7.1±0.09	7.5±0.11
Elongation at Break (m±s.d)	30±0.12	28±0.9	25.9± 0.6	23± 0.7	22±0.15	21± 0.11	20.5± 0.16	18.2± 0.9	15.9± 0.1
In vitro release (%CPR)	98.06	94.59	92.14	89.68	87.71	85.74	80.32	77.85	74.9
Surface pH (m±s.d)	6.56±0.13	6.78±0.17	6.81±0.127	6.87±0.15	6.75±0.148	6.69±0.16	6.82±0.12	6.84±0.18	6.65±0.20
t50	220	260	280	250	285	300	280	345	360
In vitro diffusion release	96.53	93.42	90.91	87.13	85.11	84.11	81.45	78.2	75.69
Swelling Index (m±s.d)	26.3±0.012	29.9±0.018	30.1±0.021	32.4±0.023	35±0.015	36.2±0.024	37.5±0.016	38.4±0.020	39.9±0.017
Mucoadhesive Strength (m±s.d)	10±0.49	12±0.47	13±0.31	15±0.42	18±0.45	21±0.39	22±0.48	23±0.52	25±0.50

Content uniformity

It was determined for all formulation by UV spectrophotometer method shown in **Table 5.**The data obtained from triplicate studies were analysed for mean and standard deviation. The results of content uniformity indicated that the drug was uniformly dispersed. Recovery was possible to the tune of 90.13% to 101.29 %.

Swelling studies

Assessment of the swelling behaviour was done by measuring radial swelling. F9 patches showed high radial swelling, and F1 shows lowest swelling index; the recorded swelling values after 8 hr were 26.27±0.012 to 39.85 ±0.017 shown in table 5. The swelling state of the polymer was reported to be crucial for its bioadhesive behaviour. As the polymeric content increase, swelling also increases. Increase in percentage swelling causes decrease in drug release from the buccal patch. The comparison of percent swelling shown in figure 3.

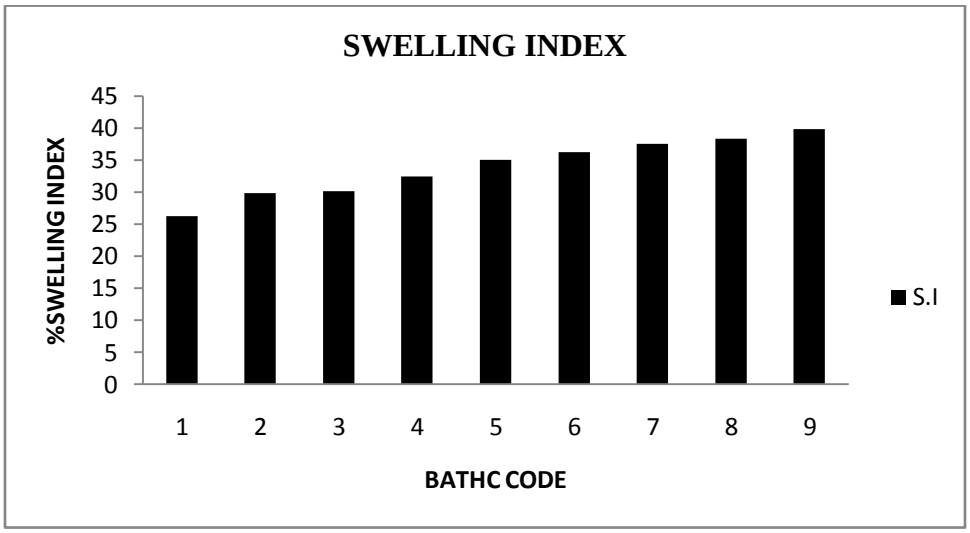


Figure 3 Swelling index of factorial batch

Surface pH

The surface pH of all formulations was nearer to neutral (≈7) and hence no mucosal irritation was expected. It should be in the range of pH 6.57±0.013 to 6.87±0.015 shown in table 5. The surface pH of buccal film were determined in order to investigate the possibility of any in-vivo side effect, as an acidic or alkaline pH may cause irritation to the buccal mucosa.

Ex vivo residence time

For *ex vivo* residence time, all patches, except patch of F1, remained attached to the mucosal surface till complete erosion (more than 480hr) shown in table 5. Longer duration was recorded for patch of F9 i.e. 518 min. All the patches retained their integrity during the study time without detachment.

In-v*itro* diffusion studies

The drug release profiles of buccal patches of carvedilol were shown in Figure 4**.** The drug release was governed by the amount of matrix forming polymer. An increase in polymer concentration causes an increase in the viscosity of the gel as well as formation of a gel layer with a longer diffusional path. This could cause a decrease in the effective diffusion coefficient of the drug and therefore a reduction in the drug release rate however, the difference is insignificant among the formulations. Formulation F1 showed maximum drug release (96.53%), where as formulation F5 showed lowest release of 75.69% among the series. Data of the *in vitro* diffusion release was fit into different equations and kinetic models to explain the release kinetics of carvedilol from buccal patches. The kinetic models used were zero-order equation, first-order equation, and Korsemeyer-Peppas models. Zero order model seemed to be the most appropriate model describing release kinetics from all patches (0.998 for formulation F1 to 0.991 for formulation F9).

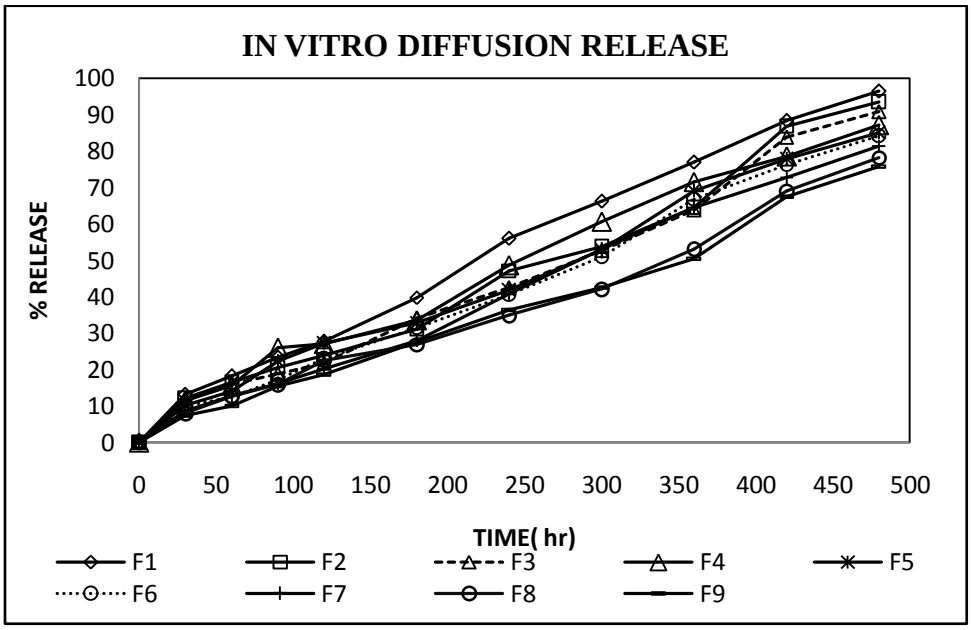


Figure 4 In vitro diffusion release of factorial batch F1 to F9

On the other hand ‘n’ values (n< 0.5) indicated that amount of released drug was by Fickian diffusion. Increasing the concentration of the polymer in the formulations showed a sustained effect on carvedilol release, but the difference is insignificant (p>0.05). This is because, as the proportion of these polymers in the matrix increased, there was an increase in the amount of water uptake and proportionally greater swelling leading to a thicker gel layer. Zero-order release from swellable hydrophilic matrices occurs as a result of constant diffusional path lengths. When

the thickness of the gelled layer and thus the diffusional path lengths remain constant, zero order release can be expected. In this investigation similar behaviour was predicted and obtained.

Measurement of Mechanical Properties

Ideal buccal film, apart from good bioadhesive strength, should be flexible, elastic and strong enough to withstand breakage due to stress caused during its residence in the mouth. The tensile strength (TS) and elongation at break (E/B) shows the strength and elasticity of the film. A soft and weak polymer is characterized by a low TS and E/B; a hard and brittle polymer is defined by a moderate TS, and low E/B; a soft and tough polymer is characterized by a moderate TS and a high E/B; whereas a hard and tough polymer is characterized by high TS and E/B.[27] The results of the mechanical properties i.e. TS and E/B are presented in Table 5. TS increased with the increase in polymeric content but E/B values decreased with the increase in polymer content. Maximum TS was exhibited by F9 patch (7.8±0.13 kg.mm–2) and minimum was exhibited by F1 (5.3±0.9 kg.mm–2). Maximum E/B was seen with F1 (30±0.12% mm–2) and the least was observed with F9 (15.9± 0.1% mm–2) as shown in table 5.

***In-vitro* Release Studies of Carvedilol from Buccal Films**

The release profiles were shown in figure 5. A perusal to figure 3 indicated that the drug release was highest in F1 i.e. 98.06% and F9 has lowest drug release. Phosphate buffer pH 6.8 and methanol 10% was used as medium for the release studies to show the drug release profile of carvedilol patches containing different ratios of polymer.

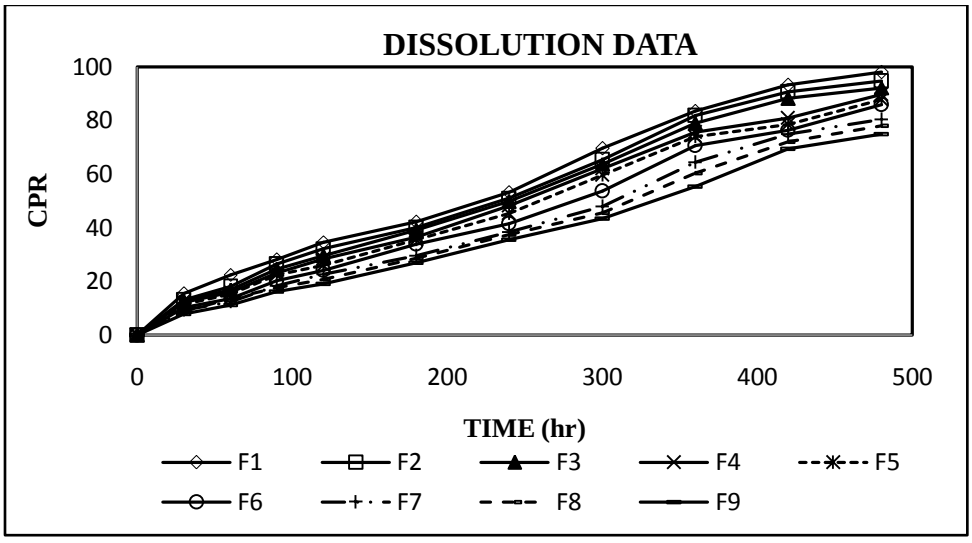


Figure 5 In vitro release studies of factorial batch of carvedilol

It is apparent from the plots that the drug release was governed by polymer content. An increase in the polymer content was associated with decrease in drug release rates. There appeared no significant difference in the final percentage of drug release. The patch (F1) released the drug

much faster than the other formulations. With F2 and F3 also showed T 50 values of less than 5 hour shown in table 5. Formulations with higher polymer content (F6, F7 and F9) have shown increased T 50 values. Increasing the amount of the polymer in the patches produced the water swollen gel like state that could substantially reduce the penetration of the dissolution medium into the patches and so the drug release was retarded.

Ex Vivo Mucoadhesive Strength

In this study, the mucoadhesive strength was determined by measurement of the force of detachment or force of adhesion. These parameters are the most frequently studied adhesive properties[28] Films made of HPMCK4M and HPC-L demonstrated to have a good in vitro adhesion property. HPC-L has negative effect on mucoadhesive strength. Among all these formulated patches, formulation F9 showed maximum mucoadhesive strength (25±0.50 g) shown in table 5.

Full and reduced model

Full and reduced model generate for dependent variable i.e. t_{50} (time required to release 50% drug), swelling index, mucoadhesive strength, in vitro diffusion release, n, and k. Surface plot also plotted for dependent variable as shown in **figure 6.**

The significance levels of the coefficients b_{11}, b_{22}, and b_{12} were found to be P= 0.0.108, 0.155, and 0.339 respectively. So they were omitted from the full model to generate a reduced model. The critical value of F for α =0.1 is equal to 9.2766 (degree of freedom=3, 3). Since the calculated value (F_{cal}= 3.6965) is less than critical value (F_{cri}=9.2766), it may be concluded that the interaction term b_{11}, b_{22}, and b_{12} do not contribute significantly to the prediction of t50 and can be omitted from the full model to generate the reduced model.

For full model:

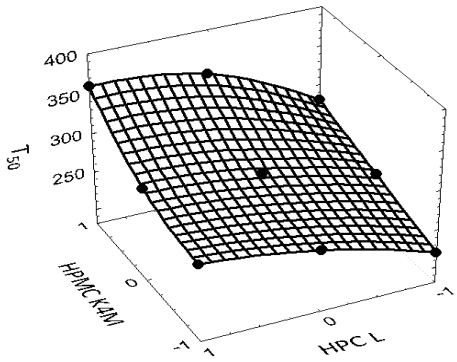
$Y= 286.66 + 35X_1 - 29.166X_2 -7.5X_1X_2 + 15X_1^2 - 12.5X_2^2$

For reduced model:

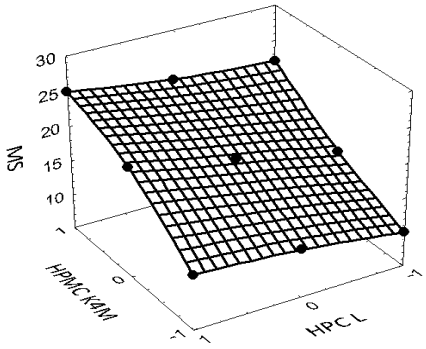
$Y= 286.66 + 37.5X_1 - 31.66X_2$

Full and Reduced Model for mucoadhesive strength

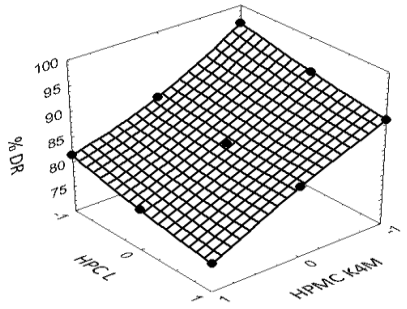
The significance levels of the coefficients b_{11}, b_{22}, and b_{12} were found to be P= 0.0.471, 0.879, and 0.655 respectively, so they were omitted from the full model to generate a reduced model. The critical value of F for α =0.1 is equal to 9.2766 (degree of freedom=3,3). Since the calculated value (F_{cal} = 0.2423) is less than critical value (F_{cri} = 9.2766), it may be concluded that the interaction term b_{11}, b_{12} and b_{22} do not contribute significantly to the prediction of mucoadhesive strength and can be omitted from the full model to generate the reduced model.



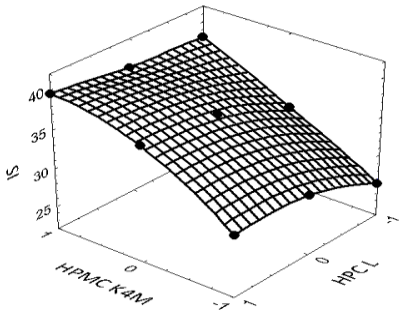
Response Surface Plot for t50



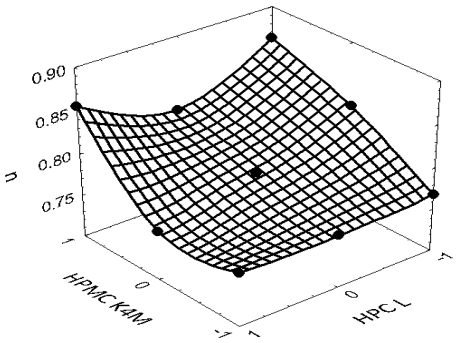
Response Surface Plot for mucoadhesive strength



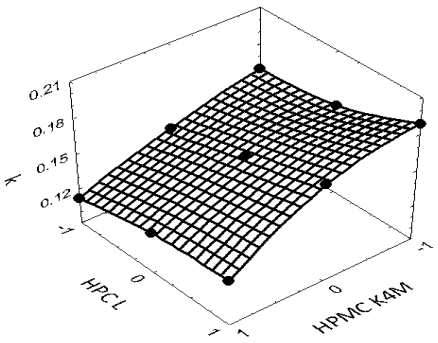
Response Surface Plot for in vitro diffusion release



Response Surface Plot for swelling index



Response Surface Plot for Diffusion Coefficient (*n*)



Response Surface Plot for Release Rate Constant (*k*)

Figure 6 Response surface plots for dependent variables i.e. mucoadhesive strength, swelling index, in vitro diffusion release, t_{50}, diffusion coefficient (n), release rate constant

Full and Reduced Model for t_{50}

For full model:

$Y= 18.08 + 5.958X_1 - 2.125X_2 - 0.375X_1X_2 - 0.625X_1^2 - 0.125X_2^2$

For reduced model:

$Y= 17.66+ 5.833X_1 - 2X_2$

Full and Reduced Model for in vitro diffusion release

The significance levels of the coefficients $b_{11,}$ $b_{22,}$ and b_{12} were found to be P= 0.541, 0.734, and 0.464 respectively, so they were omitted from the full model to generate a reduced model. The critical value of F for α =0.1 is equal to 9.1172 (degree of freedom=3, 3). Since the calculated value (F_{cal}= 0.5572) is less than critical value (F_{cri}=9.1172), it may be concluded that the interaction term $b_{11,}$ b_{12} and b_{22} do not contribute significantly to the prediction of mucoadhesive strength and can be omitted from the full model to generate the reduced model.

For full model

$Y= 85.3 -7.418X_1 + 2.231X_2 + 0.505X_1X_2 + 0.415X_1^2 + 0.225X_2^2$

For reduced model

$Y= 85.83-7.586X_1$

Full and Reduced Model for swelling index

The significance levels of the coefficients $b_{11,}$ $b_{22,}$ and b_{12} were found to be P= 0.541, 0.734, and 0.464 respectively, so they were omitted from the full model to generate a reduced model. The critical value of F for α =0.1 is equal to 9.1172 (degree of freedom=3,3). Since the calculated value (F_{cal}= 0.5572) is less than critical value (F_{cri}=9.1172), it may be concluded that the interaction term $b_{11,}$ b_{12} and b_{22} do not contribute significantly to the prediction of mucoadhesive strength and can be omitted from the full model to generate the reduced model.

For full model

$Y= 35.98+ 5.177X_1 -1.903 X_2 + 0.696X_1X_2 -1.75X_1^2 -1.15 X_2^2$

For reduced model

$Y= 34.204+ 4.945X_1 -1.671 X_2$

Full and Reduced Model for Diffusion Coefficient (n)

The significance levels of the coefficients b_2, $b_{11,}$ $b_{22,}$ and b_{12} were found to be P= 0.320, 0.559, 0.453 and 0.812 respectively, so they were omitted from the full model to generate a reduced model. The critical value of F for α =0.1 is equal to 9.1172 (degree of freedom=4,3). Since the calculated value (F_{cal}= 0.8031) is less than critical value (F_{cri}=9.1172), it may be concluded that the interaction term b_2, $b_{11,}$ b_{22} and b_{12} do not contribute significantly to the prediction of diffusion coefficient(n) and can be omitted from the full model to generate the reduced model.

For full model

$Y= 0.778+ 0.041X_1 -0.0148X_2 + 0.00506X_1X_2 + 0.0128X_1^2 + 0.0168X_2^2$

For full model

$Y= 0.799 + 0.0395X_1$

Full and Reduced Model for Release Rate Constant (K)

The significance levels of the coefficients $b11$, b_{22}, and b_{12} were found to be P= 0.178 0.6529, and 0.6060 respectively, so they were omitted from the full model to generate a reduced model. The critical value of F for α =0.1 is equal to 9.2766 (degree of freedom=3,3). Since the calculated value (F_{cal}= 0.1.556) is less than critical value (F_{cri} =9.2766), it may be concluded that the interaction term b_{11}, b_{22} and b_{12} do not contribute significantly to the prediction of release rate constant (K) and can be omitted from the full model to generate the reduced model.

For full model

$Y= 0.154 -0.025X_1 -0.0144X_2 -0.00281X_1X_2 -0.00856X_1^2 + 0.00244X_2^2$

For full model

$Y= 0.1497-0.0245X_1 + 0.0135b_2X_2$

CONCLUSION:

The buccal adhesive patch formulated from HPMCK4M and HPC-L showed satisfactory physicochemical properties. The ratio of hydrophilic polymers HPMCK4M to HPC-L had significantly influenced on its characteristics like swelling index, ex-vivo mucoadhesive strength and *in-vitro* drug release. Good correlation was observed between drug release and drug permeation study *in-vitro*. So, it can be concluded that such a mucoadhesive patches of HPMC K4M and HPC-L could be a good carrier in buccal delivery of carvedilol. It may also concluded that adhesion of buccal drug delivery device to mucosal membrane leads to an increased drug concentration gradient at the absorption site and therefore improved bioavailability of systemically delivered drug. Hence the development of bioadhesive buccal formulations for carvedilol may be a promising one as the dose of carvedilol may be decreased and hence side effects may be reduced.

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