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Evaluation of a diltiazem hydrochloride buccal bioadhesive tablet formulation

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Abstract

For the management of hypertension, a buccal bioadesive tablet containing diltiazem hydrochloride was developed. As a bioadhesive polymer, a mixture of carbopol 974 and hydroxypropyl methyl cellulose K4M was utilized. Diltiazem hydrochloride was used as a model medication, and the tablets' release was evaluated by an in vitro dissolving test. Diltiazem hydrochloride is not broken down in the liver after oral dosing, demonstrating a positive therapeutic effect. Different metrics, such as weight variation, tablet hardness, medication content, bioadhesion force, and swelling index, were used to assess the tablets' performance.

Keywords: buccal bioadhesive tablet, diltiazem hydrochloride, carbopol 974P, hydroxypropyl methyl cellulose K4M

Introduction

An alternative to traditional routes of medication administration like swallowing or injecting is buccal drug delivery.1 The advancements in buccal medication delivery have expanded the usefulness of this mode of administration. Benefits of buccal drug delivery systems over oral administration include protecting the drug from the stomach's acidic environment, avoiding the hepatic first pass effect, and taking advantage of the mucosa's high permeability and rich blood supply to increase bioavailability.2 Research into a group of polymeric compounds with purported mucoadhesive characteristics is now receiving considerable attention. Numerous attempts have been made to accomplish systemic administration of medications via the buccal mucosa, and many of them have relied on mucoadhesion. Tablets, patches, tapes, films, semisolids (ointments and gels), and powders are all examples of different types of formulations.3] Advantages of a mucoadhesive drug delivery system include the ability to target a specific area, increasing the bioavailability of the drug; increasing the residence time of the drug in the target area; and allowing for once-daily dosing by extending the residence time of the dosage form in the target area.4 Because of its rapid first-pass metabolism, short half-life (three to five hours), and low toxicity (log P = 2.79) diltiazem hydrochloride was chosen as a medication.

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X1	X2	HPMC	Carbopol
+	-	8	7.5
+	+	12	7.5
-	-	8	15
-	+	12	15

The Stuff and How We Do It

Nicholas Piramal in Mumbai supplied the diltiazem hydrochloride, while Research Lab Fine Chemical Industries in Mumbai supplied the carbopol 974P hydroxy propyl methyl cellulose K4M, citric acid, and sodium saccharine. Appasaheb Birnale College of Pharmacy in Sangli had their laboratory equipment assessed.Compositional Choice in PolymerFor buccal formulation, we employ HPMC K4M and Carbopol 974P. Placebo pills were made by combining carbopol 974P and HPMC K4M in varying concentrations. Table 1 shows the results of a 22-factorial experiment conducted with two polymer concentrations.

Table 1: Design Matrix for the formulations of placebo

2

by using 2^2 factorial design.

Formulation of medicated Tablets:

A 3^2 full factorial design was constructed where amount of HPMC K4M(X_1) and carbopol(X_2) were selected as the independent variables. The levels of two were selected on the basis of the preliminary studies which showed an optimum result for bioadhesion and swelling index. The time required for drug release at 3h, bioadhesion force (F) and studies were selected as response variables.

A statistical model incorporating attractive and polynomial terms used was to evaluate the response $Y = b_0 + b_1X_1 + b_2X_2 + b_{12}X_1X_2 + b_{11}X_1^2 + b_{22}X^2$

Where Y is dependent variable, b_0 is the arithmetic mean response of the 9 runs and b_1 is the estimated coefficient for the factor X_1. The main effect (X_1 and X_2) represents the average result of changing one factor at a time from its low to high value. The interaction term (X_1 X_2) shows how the response changes when two factor are changed simultaneously. The polynomial terms (X_1, X_2) are included to investigate nonlinearity.

Table 2: Formulation of diltiazem hydrochloride

Formulation Ingredients	Formulations and quantity (mg)								
	F1	**F2**	**F3**	**F4**	**F5**	**F6**	**F7**	**F8**	**F9**
Drug	30	30	30	30	30	30	30	30	30
Carbopol 974P	7.5	11.25	15	7.5	11.25	15	7.5	11.25	15
HPMC K4M	8	8	8	10	10	10	12	12	12
Avicel	30	30	30	30	30	30	30	30	30
Sodium Saccharin	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5
Citric acid	1.8	1.8	1.8	1.8	1.8	1.8	1.8	1.8	1.8

Lactose	71.2	67.45	63.7	69.2	65.45	61.7	67.2	63.45	59.7
Ethyl cellulose	10	10	10	10	10	10	10	10	10
Total	160	160	160	160	160	160	160	160	160

The tablets of diltiazem hydrochloride were made using the direct compression process, and were put together in this way:

First, tablets of diltiazem hydrochloride were made using direct compression methods.

The drug and the fillers were mixed together perfectly. A 6-station tablet punching machine was used to pre-compress 150 mg of the powder mix at a pressure of 0.5 ton, resulting in single-layered flat beveled tablets with a diameter of 8 mm.Third, 10 mg of ethyl cellulose powder was added, and the tablet was finally compressed at a pressure of 3.5 tons.

Each pill weighed 160 milligrams (mg). The created formulation was tested in a number of ways to ensure its quality, including for weight variation, tablet hardness, friability, tablet thickness, in vitro dissolution, in vitro bioadhesion force, study swelling index, and in situ diffusion.

Evaluation:

Vernier calipers were used to measure the thickness and diameter of a tablet. Three pills from each batch were used to get the average.Twenty pills' weights were measured independently for the Weight Variation Test. The average pill weight was calculated by adding together their individual masses. Each person's weight was compared to the mean.The toughness of a tablet was measured using the Monsanto hardness tester. The kilogram is the standard for measuring force.

Harmony in the Contents:

Five pills from each batch were ground into a powder, and then 10 mg of diltiazem hydrochloride was precisely weighed and measured before being extracted with the right amount of methanol. Each extract was properly diluted before undergoing spectrophotometric examination at 236 nm. A maximum concentration of the excipients employed in the formulation was analyzed by spectrophotometry, and it was discovered that they did not cause any interference at 236 nm in methanol.

Tests of glass dissolution:

A USP class II dissolving equipment (paddle type) was used to mix the components in vitro. A dissolving flask containing 900 ml of 6.8 phosphate buffer was maintained at 37 + 0.5 oC and 50 rpm throughout the experiment. One tablet was packaged in each individual dissolving flask. The machinery was allowed to run for three hours with no oversight. After three hours, the old medium was thrown out and the auto sampler was programmed to collect a 5-milliliter sample every 30 minutes. Absorbance at 236 nm was measured for the solution. An equation for calculating cumulative drug release was derived using standard curve data. Each of the pre-release checks was scrutinized by three individuals. For this study, we used the Indian program PCP Disso V-3.

Bioadhesion's Amazing PotentialA mucoadhesive force measuring equipment was used to evaluate the bioadhesive properties of each final formulation. Researchers looked at the bioadhesive power of the

The level of mucoadhesive polymer was determined by observing how much pressure was required to remove the formulation from one made of mucin. The mucin discs were made by compressing 250 mg of crude porcine mucin with a flat-faced punch of 8 mm diameter using a multistation rotary punch disc machine (FLUIDPACK MINIPRESS). The mucin disc was adhered to the glass vial using -cyanoacrylate adhesive. As a final step, the glass vial was fastened to the right arm of the inverted balance. Distilled water was used to wet a mucin disc before bioadhesion testing was performed. The pills were stored in the lower vial, and the top vial was elevated until the disc of mucin came into contact with the pills. BothTo facilitate the formation of an adhesive bond, the pill and the hydrated mucin disc were brought into contact with a preload of 10 g and held for 2 minutes. Preload time and force were remained constant across all of the iterations. After the allotted time for the balance to zero out, water was poured from a glass bottle into a plastic jar on the left pan of the scale at a rate of 30 drops per minute using an infusion set. After removing the mucin disc from the sample under test, water addition was stopped, the plastic jar was reweighed, and the weight difference was utilized to calculate the amount of water required to dissolve the disc. They provided the averages of three separate tests.

The following formula may be used to determine the Bioadhesive Force:

$$F = 0.00981 \, {}^{W}/_{2}$$

W = Amount of Water

Swelling index:

Tablets were weighed individually (designated as w_1) and placed separately in petridishes containing phosphate buffer 6.8 pH. At regular intervals (0.5, 1, 2, 3, 4 h), samples were removed from the petridish and excess water was removed carefully by using filter paper. The swollen tablets were reweighed (w_2). The swelling index of each system was calculated using the following formula:

This is because a greater distance must now be traveled via the diffusion pathway. Increasing the amount of polymer causes a more gradual release of the drug. This may be because, as hydrogel concentration rises, the gel layer around the tablet has a greater tendency to inhibit the release of the active component. Carbopol's presence in the formulation significantly reduces drug release, making its impact more obvious than HPMC's. This might be because more water is being absorbed by the polymer. Carbopol, which retains water inside its matrix and inhibits medicine release, exhibits a similar behavior as it swells. [ix] The lowest polymer content in the F1 formulation allows for the most efficient drug release. Increases in carbopol content in F8 and F9 formulations reduce the rate of drug release.

The bioadhesion force varies significantly with carbopol content. It was discovered that when HPMC concentration increased, so did the bioadhesion force. The weakest bioadhesion force was seen with formulation F1, whereas the greatest was observed with formulation F9. Excessive amounts of carbopol and HPMC might be to blame. An increase in adhesion sites and, by extension, force, seems to occur at a greater carbopol ratio. Two polymers used together provide the strongest adhesion possible. The reason why intermolecular complexation between HPMC and carbopol works so well is because the latter may absorb water and get trapped inside the former's network. [x]

Measure of swelling:

The polymer's swelling capacity is measured using a metric called the swelling index. The concentration of the polymer has a significant effect on the swelling index. The swelling index increases with increasing polymer concentration, which may be because of greater water uptake by the polymeric matrix. Both polymers are hydrophilic, meaning they can absorb and retain water.

Research on Optimisation:

To determine the impacts of several elements and their interactions, researchers often use factorial designs. Nine tests are needed for a two-factor, three-level experiment. Drug release, bioadhesion force, and swelling index were all studied using this method to calculate the precise impact of formulation parameters. Both carbopol and HPMC concentrations were used as independent variables. To ensure that the runs could be carried out at the operational units required by the factorial design, preliminary tests were undertaken to establish the operational formulation range that would successfully deliver bioadhesion and swelling. Examining the information in Table 2 allowed for qualitative estimations of the impact of the different factors. Visually, it would be hard to anticipate whether or not the interactions between the variables truly occurred, or to identify which individual variable had the most significant influence. The given standardised Pareto Chart has bars for each effect, ordered from greatest to least. Each bar's height corresponds to the t-statistic that would be used to determine whether or not the impact is statistically significant. At the point when Student's t reaches significance levels of 0.05, a vertical line is drawn. Statistically significant results at the 5% level are shown by the presence of bars that lie to the right of the line. Carbopol concentration was shown to substantially alter all the responses across the board. The data showed that a linear reduction in drug release from formulations occurred when the concentration of carbopol was increased. As the concentrations of Carbopol and HPMC were raised, the bioadhesion force and swelling also rose. F1 and F2 formulations were shown to have excellent drug release but minimal bioadhesion force and edema. Drug release was slowed down in formulations F6, F7, F8, and F9 when the polymer content was increased, yet bioadhesion was at its highest. Although bioadhesion and swelling were enhanced in formulations F3 and F4, formulation F5 demonstrates superior drug release, bioadhesion force, and swelling index. Based on the findings of our research, we conclude that the formulation F5 is the best option.

Evidence from this research reveals that carbopol and HPMC were used to produce a buccoadhesive tablet of diltiazem hydrochloride with a controlled release time of up to 3 hours. The bioadhesive power of the pill was quite high. The outcomes of using the factorial optimization method are very predictable and realizable. Formulation F5 was the most effective of the formulations tested in this investigation. Therefore, the research may help the formulator get closer to and even quantify the

optimal, cutting down on trial-and-error during formulating.

Table 3: Weight variation, thickness, diameter, hardness, drug content

Formulation batches	Weight uniformity (mg)	Thickness (mm) ± Sd	Diameter (mm)	Hardness (Kg/cm^2)	Drug content (%)
F1	160.85	1.4±0.01	8	4-5	98.41
F2	160.49	1.5±0.02	8	4-5	99.70
F3	159.2	1.4±0.02	8	4-5	99.65
F4	160.5	1.4±0.02	8	4-5	100.47
F5	161.4	1.5±0.02	8	4-5	99.21
F6	161.9	1.6±0.02	8	4-5	101.32
F7	161.7	1.4±0.03	8	4-5	99.35
F8	162.6	1.5±0.02	8	4-5	101.31
F9	163.6	1.6±0.03	8	4-5	98.20

Table 4: % Cumulative Release of Formulation F1 – F9

	% Cumulative Release									
Sr.No	Time(min)	F1	F2	F3	F4	F5	F6	F7	F8	F9
1	0	0	0	0	0	0	0	0	0	0
2	30	34.5	36.9	32.9	39.6	41.2	41.0	33.9	32.4	27.8
3	60	44.5	48.5	47.7	49.8	50.1	47.6	43.1	37.3	33.8
4	90	60.6	61.2	60.2	63.8	61.8	57.2	49.1	48.5	46.4
5	120	63.9	72.2	70.2	73.5	74.0	65.1	64.3	64.4	60.4
6	150	74.8	83.3	81.4	85.4	85.7	79	74.6	72.9	70.1
7	180	97.2	92.2	86.4	94.1	95.1	83.4	91.3	85.0	81.2

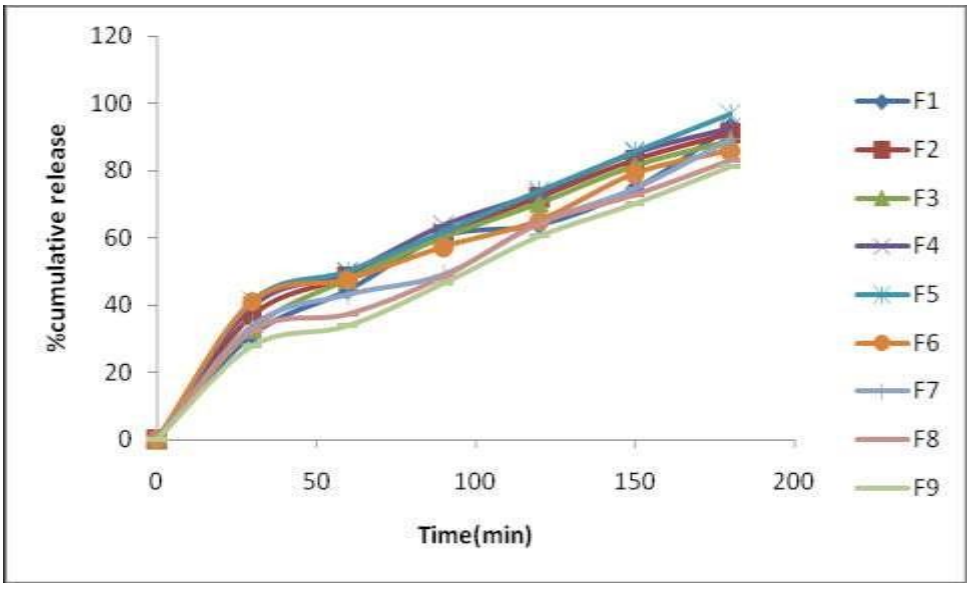


Figure 1: % Cumulative Release of Formulation F1 – F9

Table 5: Bioadhesive Force of formulation F1 – F9

Formulation	Bioadhesion Force (N)
F1	0.0325±0.011
F2	0.0426±0.009
F3	0.0551±0.015
F4	0.0591±0.014
F5	0.06925±0.016
F6	0.0859±0.021
F7	0.0613±0.013
F8	0.0765±0.02
F9	0.1104±0.01

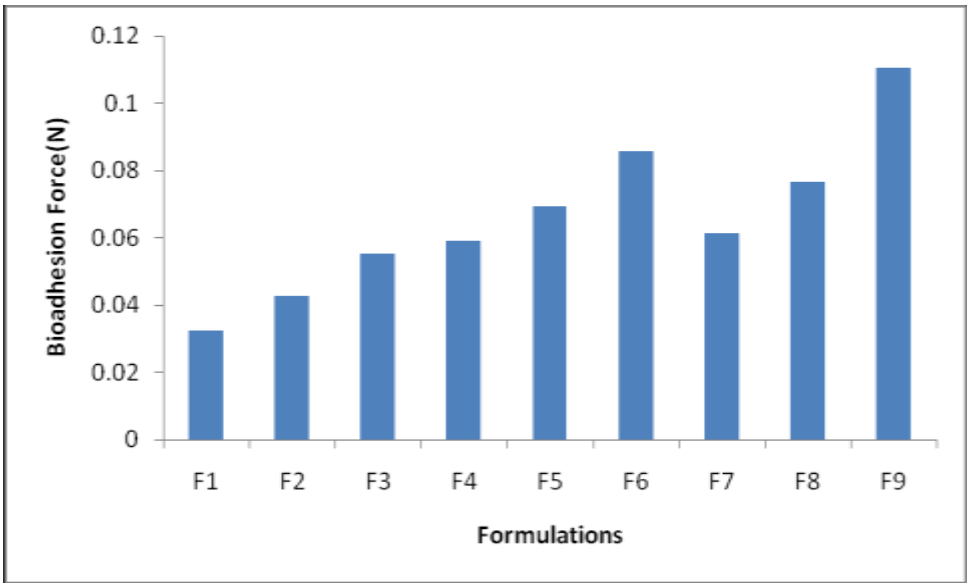


Figure 2: Bioadhesive Force of formulation F1 – F9

Table 6: Swelling index of formulation F1 – F9

Formulation	%Swelling index
F1	65.34
F2	68
F3	72.34
F4	69.24
F5	85.12
F6	86.72
F7	74.83
F8	90.26
F9	92

Figure 3: Swelling index of formulation F1 – F9

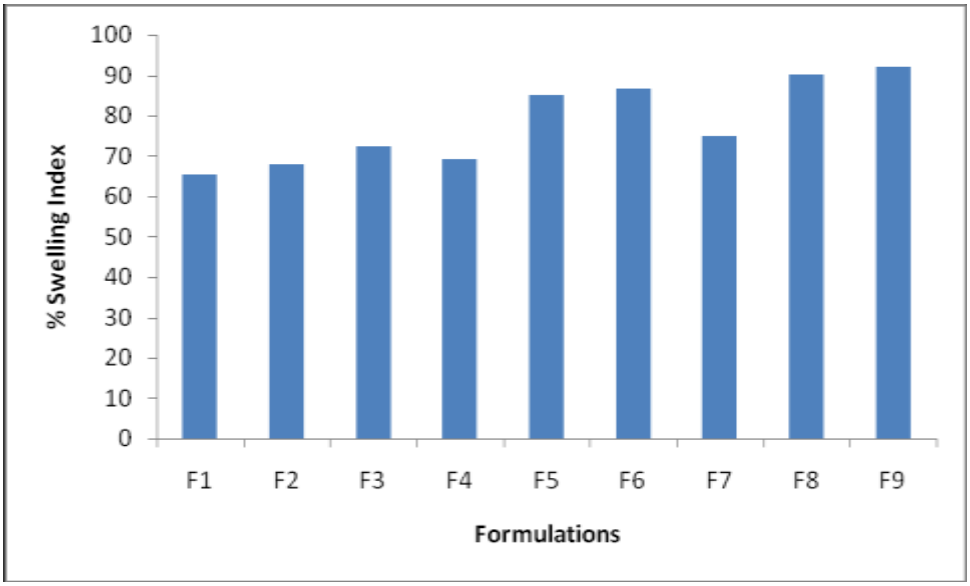
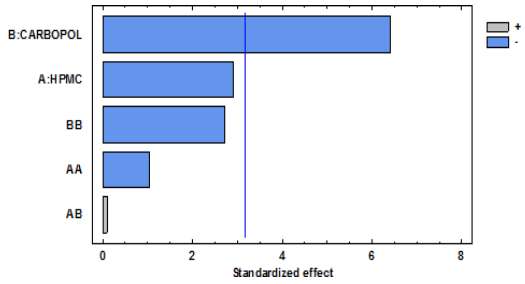
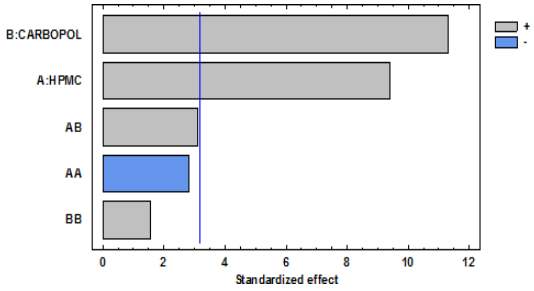


Table 7: Design Matrix for the formulations of diltiazem hydrochloride by using 3^2 factorial design

Formulation	Independent Variables		Actual Values		Response Variables		
	X_1	X_2	X_1	X_2	Y_1-Rel_{3h} (%)	Y_2-F (g)	Y_3-%S
F 1	-1	-1	8	7.5	97.11	0.0325	65.24
F 2	-1	0	8	11.25	92.91	0.0426	68
F 3	-1	1	8	15	86.63	0.0551	72.34
F 4	0	-1	10	7.5	94.12	0.0597	69.85
F 5	0	0	10	11.25	95.18	0.0692	85.12
F 6	0	1	10	15	83.89	0.0853	86.72
F 7	1	-1	12	7.5	91.41	0.0713	74.83
F 8	1	0	12	11.25	89.86	0.0765	90.26
F 9	1	1	12	15	81.30	0.1104	92





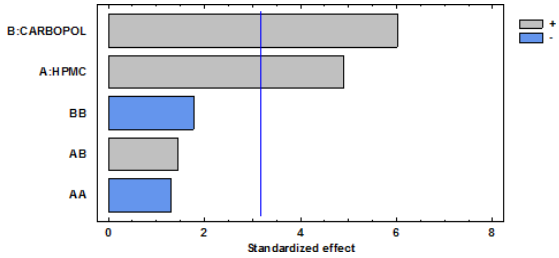


Figure 4 (Left): Drug Release
Figure5 (Right): Bioadhesion Force
Figure 6 (Below): Swelling Index

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