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DESIGN, FABRICATION, AND EVALUATION OF BUCCAL DRUG DELIVERY OF BENIDIPINE HYDROCHLORIDE

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Keywords:

Buccal drug delivery, Benidipine Hydrochloride, Carbopol 934, HPMC, Calcium channel blocker, Extended release

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ABSTRACT: The present study involves the formulation development and *in-vitro* evaluation of benidipine hydrochloride buccal tablets. Designed to prolong the time of release of drug and also to enhance the better bio-availability of the drug. Benidipine hydrochloride is a long-acting calcium channel blocker. It exerts its antiangial, antihypertensive action through blocking the influx of ca ions through voltage gated L-type ca channels to the pheripheral vascular smooth muscle cells, coronary smooth muscle cells and to the myocardial cells. And having biological half life 1-2 hrs, extensive protein binding need to formulate an dosage form. Benidipine hydrochloride buccal tablets were prepared by using direct compression method. Total eight formulations were prepared by using different polymers *viz.*, Sodium alginate, Chitosan, Carbopol 934, HPMC, in various ratios. The nature of the polymer influences the physical and release characteristics of the buccal tablets. Preformulation studies were carried out before formulation design. Preformulation results showed good flow properties and all results are within specified limits. Compatibiity for drug and excipient was carried by FT-IR and result was showed no interaction. *In-vitro* dissolution studies was carried out by using 6.8 phosphate buffer. All the formulations showed good dissolution profiles. In Among all the formulation (F1-F8), F7 Containing carbopol 934 with HPMC, showed better mucoadhesive strength (28.80) and release of drug (99.92%) from buccal tablet for 6 hour was observed.

INTRODUCTION: When compared to parenterals, injectable buccal drug delivery is preferable and has a number of advantages over other routes. Patients may experience some discomfort with the peroral approach. As a result, for the immediate release of drug and for instant release at the desired region where the drug is absorbed, distributed and metabolized.

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Other administration methods are created as a result of this constraint. The buccal mucosa has an absorptive function and provides numerous advantages, including avoiding the first pass effect and increasing bioavailability through a non-invasive route. It also makes it feasible for a quick action and minimizes side effects [1].

The buccal drug delivery technique is widely used because it offers a number of benefits, a control release mechanism with an immovable surface is provided by buccal regions. Buccal mucosa favors a valuable measure by overcoming disadvantages and as a convenient route for the administration in the treatment of local or systemic therapies. Due to salivary production and composition, buccal drug

distribution serves as a possible site for chemical alteration in chronic systemic therapy. Bioadhesive polymers can sustain the effectiveness of multiple medications and have a lengthy contact period with the tissues. The controlled medication delivery products have improved bioavailability, excellent patient compliance, and cheap cost [2].

A calcium channel blocker with a long half-life is Benidipine hydrochloride. By limiting the inflow of calcium ions through voltage-gated L-type calcium channels to peripheral vascular smooth muscle cells, coronary smooth muscle cells, and myocardial cells, it exerts its antiangial, antihypertensive activity. With a biological half-life of 1-2 hours, significant protein binding necessitates the creation of a dosage form with a prolonged release [3].

MATERIALS AND METHODS: Benidipine HCl is a gift sample from Trinity Pharma Labs, Hyderabad, India. CP934, HPMC, Spray Dried Lactose, Mannitol was purchased from S.D. Fine chemicals, Mumbai, India. All other ingredients used were of analytical grades.

Drug and Polymer Compatibility Studies [4]:

Compatibility Study by FT-IR: Using a Fourier Transform Infrared spectrophotometer, the infrared spectra of a pure active ingredient (Benidipine HCl) and a physical mixture of formulations (drug and excipients) in a ratio of 1:1 were recorded. Using dried potassium bromide as a baseline correction, the spectra of the pure medication, polymer, and formulation combination were recorded on FTIR. The information is shown in **Fig. 1, 2** & **3**.

FTIR Spectra of Pure Drug Benidipine HCl:

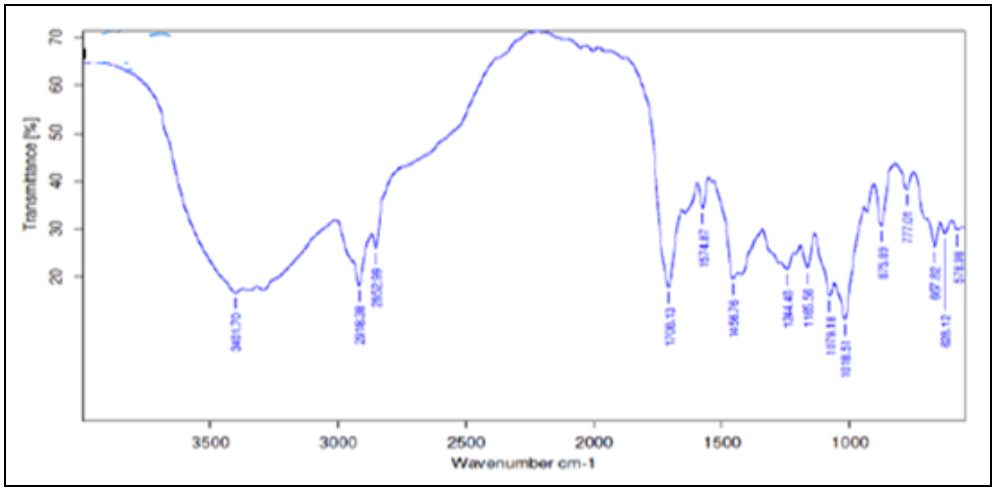

FIG. 1: FTIR SPECTRA OF PURE DRUG BENIDIPINE HCL

FT-IR spectra of Benidipine HCl and Carbopol 934:

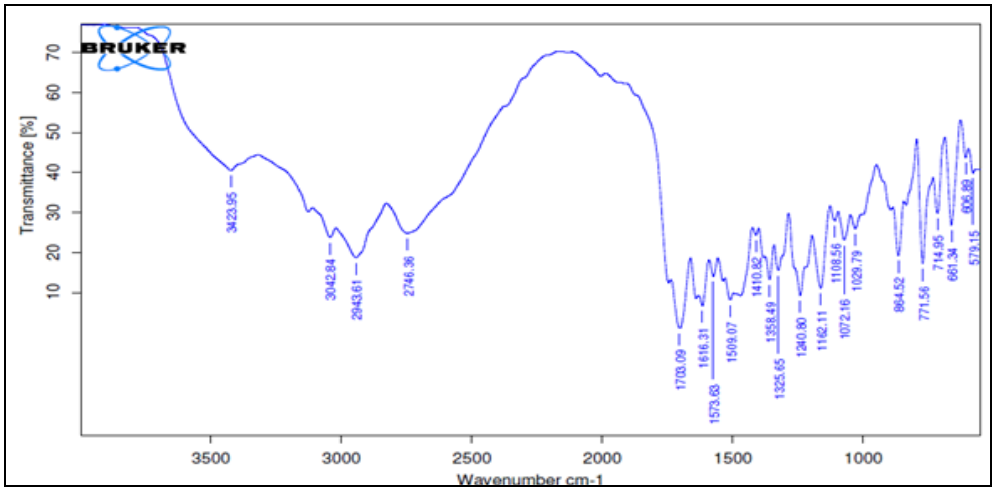

FIG. 2: FT-IR SPECTRA OF BENIDIPINE HCL AND CARBOPOL 934

FT-IR Spectra of Benidipine HCl and HPMC:

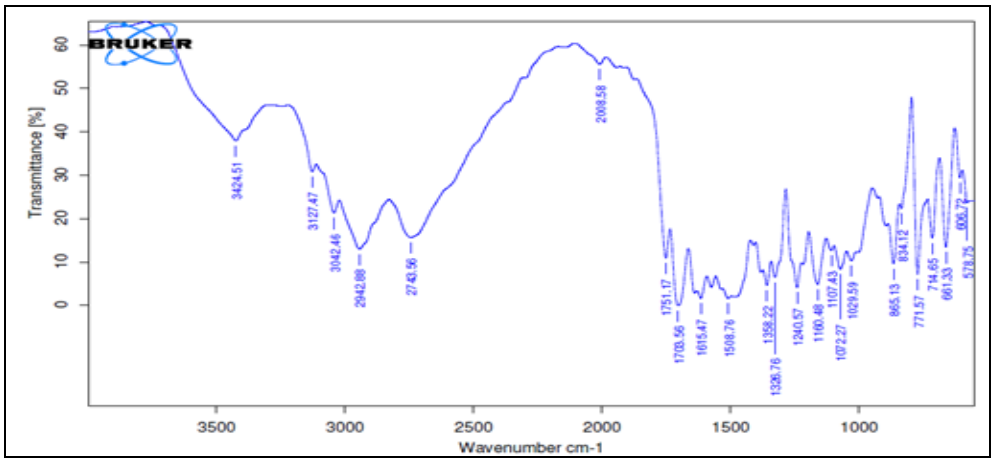

FIG. 3: FT-IR SPECTRA OF BENIDIPINE HCL AND HPMC

Method of Benidipine Buccal Tablet Preparation: Preparation of Benedipine HCl tablets containing 4 mg, by the direct compression method according to the formula mentioned in the **Table 1**. The composition of various formulations (F1 to F8) are manufactured by using HPMC and Carbopol 934P. To get a content uniformity, all of the formulation's ingredients were mixed for 15 minutes in a mortar and pestle. Then the blended formulations are compressed in 10-station rotary tablet machine with an 8mm round flat punch, and the weight of the tablet was adjusted to 160 mg.

TABLE1: FORMULATIONS (F1 TO F8) OF BENIDIPINE HYDROCHLORIDE BUCCAL TABLETS

Ingredients (mg)	F1	F2	F3	F4	F5	F6	F7	F8
Benidipine HCl	4	4	4	4	4	4	4	4
Carbopol 934	10	15	20	25	10	15	20	25
HPMC	80	75	70	65	90	85	80	75
chitosan	10	10	10	10	-	-	-	-
Spray dried Lactose	40	40	40	40	40	40	40	40
Mannitol	10	10	10	10	10	10	10	10
Magnesium Stearate	4	4	4	4	4	4	4	4
Talc	2	2	2	2	2	2	2	2
Total Weight (mg)	160	160	160	160	160	160	160	160

Evaluation of Benidipine Buccal Tablets: Weight variation: Weight variation test for the tablets was done as per the standard procedure in Pharmacopoeia. 10 tablets from the all the formulations (F1 to F8) were weighed in a digital balance and average weight and standard deviation were calculated. The results are shown in **Table 2.**

Thickness [5, 10]: The thickness for prepared tablets, from each formulation was determined by using a Vernier calipers. From the values, the average thickness and standard deviation for all formulations were calculated, .and the results were shown in **Table 2.**

Hardness [5, 10]: Hardness of the tablets was measured by using Monsanto hardness tester. It is a measuring the force required to break the tablet. The results are shown in **Table 2.**

Friability [5, 13]: Friability is the measured by using a Roche friabilator, It is the ability of a tablet to withstand mechanical shocks, and the test is carried by keeping 20 tablets in a plastic chamber, the revolutions are adjusted to 25 rpm, for 4 minutes. The weight of the tablets before and after friability test weighed, % of friability is calculated by following formula. The results are shown in **Table 2.**

Friability (%) = Initial weight of 10 tablets – final weight of 10 tablets / Initial weight of 10 tablets x 100

Determination of Mucoadhesive Strength [5, 11]: Mucoadhesive strength is determined by using a modified physical balance. It is the tensile force required breaking the adhesive bond between the mucous membrane and the polymer. And is important for the assessment of buccal residence

time. The results for all formulations are shown in **Table 2.**

Drug Content Uniformity [5, 10]: tablets from each formulation were triturated to get a fine powder, and equivalent weight to 100 mg of Benidipine HCl was weighed and transferred into a volumetric flask and was dissolved in a pH 6.8 phosphate buffer. The absorbance of this solution was measured at 239nm by using UV Visible spectrophotometer and compared with the standard value. The results are shown in **Table 2.**

Swelling Studies [5, 12]: The tablet weight (W1) noted before conducting the study and placed in a petri dish (containing 4 ml of pH 6.8 phosphate buffer). After 2 h, the tablet was removed and the excess water in the petri dish was removed carefully using filter paper. The weight of the swollen tablet was weighed and noted (W2). The swelling index was calculated according to the following formula. The results are shown in **Table 2.**

Swelling index (%) = (W2 – W1) /W1 x 100

***In-vitro* Dissolution Study [6]:** The *in-vitro* dissolution study was conducted in the dissolution test apparatus-II (paddle type), in a 900 ml of pH 6.8 phosphate buffer dissolution media vessel and the temperature was set for 37 ± 0.5°C. The speed of the paddle was maintained 50 rpm. 5 ml of the sample was withdrawn and the same amount of fresh medium was replenished to the dissolution medium. Samples were collected in regular time intervals (0, 0.5, 1, 2, 3, 4, 5, 6 & 7 h). And the sample's absorbance was measured by UV spectrophotometer at 237 nm. The results are shown in **Fig 4** & **5.**

Mathematical Modelling of Benidipine HCl Buccal Tablets [6, 14]: The release kinetics of a drug from the systems may predict the solute release rate and solute diffusion behaviour from polymer matrix. And to know the mechanisms of solute transport by the release data with mathematical models. The results are shown in **Fig 6, 7, 8** & **9.**

TABLE 2: EVALUATION OF BENIDIPINE HYDROCHLORIDE BUCCAL TABLETS

S. no.	Evaluation parameter	F1	F2	F3	F4	F5	F6	F7	F8
1	Weight variation (mg)	159 ±0.20	159 ±0.03	158 ±0.07	157 ±0.06	159 ±0.04	158 ±0.06	157 ±0.04	159 ±0.09
2	Thickness (mm)	2.44 ±0.05	2.51 ±0.02	2.63 ±0.06	2.55 ±0.04	2.81 ±0.04	2.55 ±0.02	2.69 ±0.05	2.80 ±0.02
3	Hardness (Kg/ cm^2)	4.1±0.1	4.±0.3	3.9±0.8	4.1±0.4	4.2±0.7	4.5±0.5	4.5±0.1	4.4±0.8
4	Friability (%)	0.62 ±0.01	0.65 ±0.02	0.64 ±0.03	0.69 ±0.03	0.62 ±031	0.63 ±0.21	0.61 ±0.13	0.64 ±0.46
5	Mucoadhesive strength (g)	17.75 ±0.53	18.29 ±0.25	23.99 ±0.23	25.40 ±0.18	26.70 ±0.23	28.25 ±0.20	28.80 ±0.23	29.45 ±0.15
6	Drug content (%)	97.80 ±0.46	96.90 ±0.66	98.65 ±0.64	97.85 ±0.98	97.65 ±0.42	98.75 ±0.46	98.90 ±0.60	99.15 ±0.56
7	Swelling index (%)	75.60 ±2.05	81.65 ±0.63	83.63 ±1.26	88.75 ±1.83	78.42± 6.26	87.64± 3.44	88.67± 4.18	88.18±5. 68

TABLE 3: CUMULATIVE % DRUG RELEASE OF BENIDIPINE HCL BUCCAL TABLETS FORMULATIONS FROM F-1 TO F-8

S. no.	Time (Hrs)	Cumulative % Drug release ± SD, n=6							
		F-1	F-2	F-3	F-4	F-5	F-6	F7	F8
	30 minutes	3.95	3.76	2.99	2.18	3.06	3.92	4.25	3.93
2	1	23.34	21.44	20.94	18.57	19.87	28.11	30.87	23.46
3	2	43.75	40.37	36.13	32.96	38.75	45.36	49.45	44.42
4	3	63.98	58.41	54.77	40.11	47.69	63.71	69.21	57.15
5	4	78.75	66.39	58.92	50.31	59.25	76.18	82.26	74.88
6	5	81.34	75.55	73.06	60.47	66.45	93.16	95.14	80.22
7	6	89.56	79.76	79.82	76.63	90.66	95.68	98.92	97.65
8	7	-	92.73	90.93	79.15	74.88	-	-	-

Graphical Representation of Cumulative % Drug Release of Benidipine HCl Buccal Formulations from F-1 to F-8: The above figure shows the *in-vitro* release profiles of Benidipine HCl buccal tablets of formulations F1 to F8. The release of the drug from the tablet was release up to

98.92% for F7 in 6 h, so the polymer is not having the capacity to extend the release up to 7 h. The above figure shows the *in-vitro* release profiles of Benidipine HCl buccal tablets of formulations F1 to F8. Effect of polymers on the release profile of Benidipine HCl was studied.

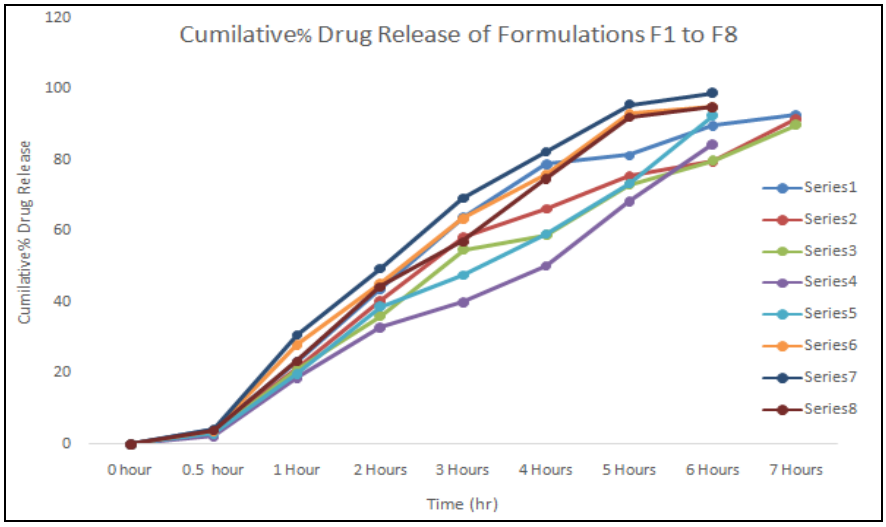

FIG. 3: GRAPHICAL REPRESENTATION OF CUMULATIVE % DRUG RELEASE OF BENIDIPINE HCL BUCCAL FORMULATIONS FROM F1 TO F8 (SERIES 1-8)

Mathematical Modelling of Bucco-adhesive Tablets [8]: Mathematical modelling of the release kinetics of specific classes may be used to predict solute release rates from and solute diffusion behavior through polymers. And elucidate physical mechanisms of solute transport by simply comparing the release data to mathematical models.

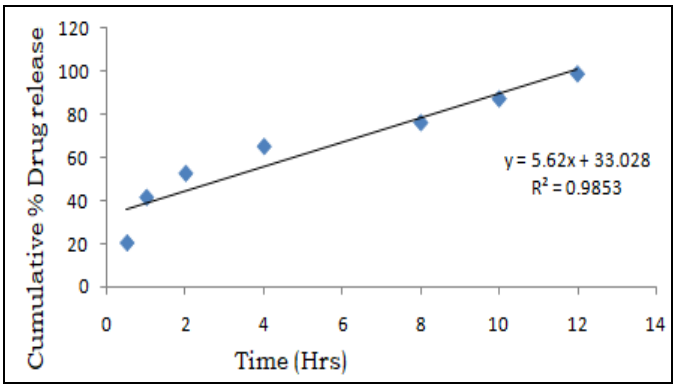

FIG. 6: ZERO-ORDER PLOT FOR OPTIMIZED FORMULATION (F7)

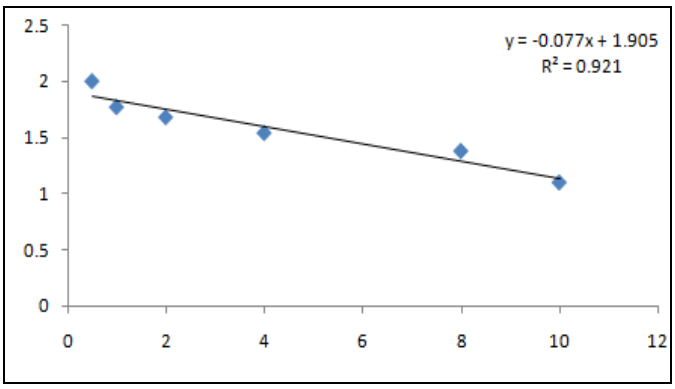

FIG. 7: FIRST-ORDER PLOT FOR OPTIMIZED FORMULATION OF BENIDIPINE HCL (F7)

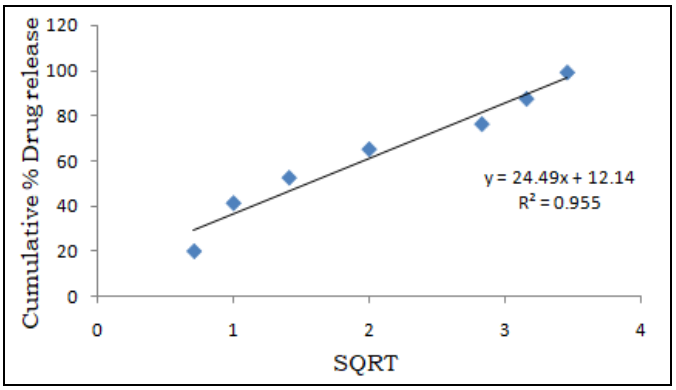

FIG. 8: HIGUCHI EQUATION MODEL FOR BENIDIPINE HCL OPTIMIZED FORMULATION (F7)

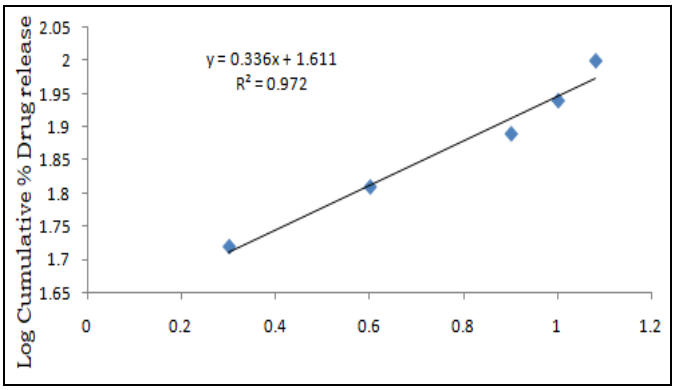

FIG. 9: KORSEMAYER-PEPPAS MODEL FOR BENIDIPINE HCL OPTIMIZED FORMULATION (F7)

TABLE 3: RELEASE KINETICS OF BENIDIPINE HCL OPTIMIZED FORMULATION (F7)

Formulation	Zero order (r^2)	First order (r^2)	Higuchi model (r^2)	Korsmayer-Peppas model		Best fit model
				r^2	"n"	
F7	0.985	0.921	0.955	0.972	0.336	Zero order

From the above results it is apparent that the regression coefficient value closer to unity in case of Zero order plot i.e. 0.985 indicates that the drug release follows a Zero order mechanism and in Korse mayer peppas plot i.e. 0.972 and further the n value obtained from peppas plot i.e. 0.336 suggest that the drug release from tablet was anomalous non-fickian diffusion. The mass transfer with respect to square root of time was plotted, revealed a linear relationship with regression value close to one i.e. 0.955 stating that the release from matrix was through diffusion.

RESULTS & DISCUSSION: Drug-polymer compatibility study for Benidipine HCl was carried out by FT-IR spectrophometer, data was shown in **Fig. 1, 2** & **3**, which indicates that there is no interaction between drug and excipients used in the formulation. Compressed Benidipine HCL buccal tablets were evaluated for thickness, hardness, friability, weight variation, swelling index, drug content and mucoadhesive strength. And results were shown in **Table 2.** In all formulations, the hardness were 3.9-4.5 kg/cm^2 & fribility was less than 1%, which indicates that all tablets has good mechanical strength. The mucoadhesive strength was found to be 17.75 to 29.45%. *In-vitro* dissolution tests were carried out using USP type-II (Paddle) apparatus using 900 ml of pH 6.8 phosphate buffer as dissolution media, drug release study carried for 7 hrs, results were shown in **Fig. 3.** The formulation F7 showed 98.92% drug release in 6 hrs and was considered as optimized formulation. The *in-vitro* release data for F7 was subjected to Zero-order, First-order, Higuchi & Korsmayer-Peppas models in order to establish the drug release mechanism & kinetics of drug release from the matrix through diffusion. Results were shown in **Fig. 6** to **9** and **Table 3.**

CONCLUSION: Benidipine Hydrochloride buccal tablets were prepared by using carbopol 934, HPMC and chitosanpolymers. FT-IR studies revealed that there was no drug-excipient incompatibility. Formulation F7 was optimized based on the release of a drug for 6 hours of time, swelling index and mucoadhessive strength. The drug release mechanism was anomalous diffusion i.e diffusion and erosion. Hence, buccal Tablets of Benidipine Hydrochloride has ensured the satisfactory drug release with the help of polymers and thereby avoid first pass metabolism, and increased the bioavailability of a drug.

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CONFLICTS OF INTEREST: The authors declare that there are no conflicts of interest.

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