WORLD JOURNAL OF PHARMACEUTICAL RESEARCH
SJIF Impact Factor 8.084
Volume 10, Issue 6, 1446-1457. Review Article ISSN 2277– 7105

FORMULATION DEVELOPMENT AND IN-VITRO EVELUATION OF BUCCAL TABLETS OF BENIDIPINE HCL TABLET

[1]*N. Rajitha, [2]M. Shiroja, [3]V. Lokesh Babu and [4]A. Srinivasa Rao

Dept. of Pharmaceutics, Bhaskar Pharmacy College, Bhaskar Nagar, Moinbad(M), RR Dist. Telangana.

Article Received on
20 April 2021,

Revised on 10 May 2021,
Accepted on 31 May 2021

DOI: 10.20959/wjpr20216-20515

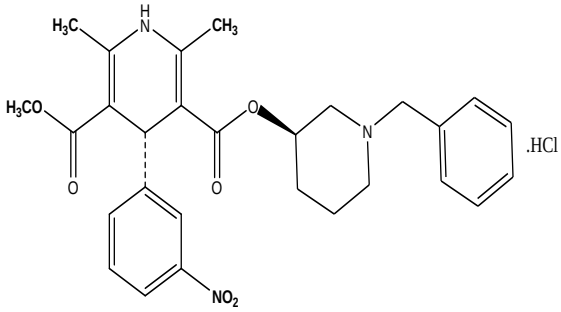
***Corresponding Author**
N. Rajitha
Dept. of Pharmaceutics,
Bhaskar Pharmacy College,
Bhaskar Nagar,
Moinbad(M), RR Dist.
Telangana.

ABSTRACT

The aim of the present study was formulation development and in-vitro evaluation of benidipine hydrochloride tablet of strength 4 mg. Direct compression technique was chosen to develop a finished pharmaceutical product. Various formulations (F1-F8) were taken. In these trials, drug: excipient ratio was varied and the effect of diluents, and various polymers like, HPMC 15 cps as a rate controlling polymer, and Sodium Alginate, Chitosan, Carbopol 940 are as mucoadhesive polymers on the performance tablets was studied.All the formulation has hausner's ratio between the 1.10 to1.18. It indicates all the formulation show better flow property. Among all formulation F7 showed in-vitro drug release 98.9% for 12hrs. And which is showed better release than marketed preparation hence considered as most promising preparation.

KEYWARDS: Benidipine Hydrochloride tablet, HPMC 15 cps as a rate controlling polymer, and Sodium Alginate, Chitosan, Carbopol 940, mannitol, lactose, magnesium stearate, talc.

1. Drug profile: Benidipine hydrochlorideis a new calcium channel blocker of the dihydropyridine type. It is used as antihypertensive and antianginal agent. It is not official in any Pharmacopoeia.



Benidipine is a long acting dihydropyridine Ca channel blocker. It exerts it`s antianginal, antihypertensive actions through blocking the influx of Ca ions through voltage gated L-type Ca channels to the peripheral vascular smooth muscle cells, Coronary smooth muscle cells and to the myocardial cells. Thus causes dilatation of vascular endothelium, decrease peripheral resistance, & reduce myocardial oxygen demand.

2.1 Solubility studies: The solubility of Benidipine was determined at room temperature in water.

2.2 Fourier transform infra-red (FTIR) spectroscopy: Infrared spectrum of Benidipine HCl was determined on Fourier Transform Infrared spectrophotometer (Bruker) using KBr dispersion method. The base line correction was done using dried potassium bromide.

2.3 Drug -Polymers compatibility study: Drug-polymer compatibility studies were done by FTIR study. FTIR spectroscopy is used to study drug- excipient interactions. The drug and polymer mixtures of Benidipine are prepared at different ratio. A base line correction was made using dried potassium bromide. The spectra of the dried mixture of drug, formulation mixture and potassium bromide were recorded and then the spectra of the dried mixture of drug, formulation mixture and potassium bromide were recorded. The resultant disc was mounted in a suitable holder IR spectrophotometer and the IR spectrum was recorded from 4000 per cm to 450 per cm. The resultant spectra were compared for any spectral changes.

2.4: Analytical methods for estimation of Benidipine HCl

2.4.1: Determination of absorption maximum of Benidipine: Various concentration of samples were taken one by one and the maximum peak of UV graph was analyzed .From the UV spectrophotometric analysis, it was conclude that the drug Benidipine showed a λ max at 239 nm. The observed λ max was used for further work to analyze the test samples.

2.5: Standard curve of pure drug Benidipine at phosphate buffer pH 6.8

Preparation of phosphate buffer pH 6.8: About 28.80 g of disodium hydrogen phosphate and 11.45 g of potassium dihydrogen phosphate was weighed accurately and dissolved in sufficient water to produce 1000m.

Procedure: 100 mg of drug was dissolved in 1000 ml of media purified phosphate buffer to give 100µg/ml. The different dilutions were made using stock solution prepared. 0.2 ml, 0.4 ml, 0.6 ml, 0.8 ml&1.0 ml of stock solution was taken and made up to 10 ml purified water to get 2, 4, 6, 8, &10µg/ml concentrations. Absorbance of diluted solutions was taken by using UV – Spectrophotometer at 239 nm wave length, using phosphate buffer as blank.

3. PREFORMULATION STUDY

3.1 Evaluation of Buccal Tablets: The prepared tablets were subjected for various quality control tests in order to characterize them.

A. Average Weight and Weight Variation: Ten buccoadhesive tablets from each batch were weighed in sartorius digital balance and average weight was determined and standard deviation was calculated.

B. Average Thickness: The thickness of ten buccal tablets in each batch was determined using a digital vernier caliper. The average thickness and standard deviation was calculated.

C. Hardness: It is tested by measuring the force required to break the tablet across the diameter. The force is measured in kg/cm^2 and the hardness of about 4 kg/cm^2 is considered to be satisfactory for uncoated tablets.

D. Friability: The weight of 10 tablets was noted and placed them in Roche friabilator. The device subjects the tablets to the combined effect of shock and abrasion by utilizing a plastic chamber, which revolves at 25 rpm, dropping the tablets a distance of 6 inches with the revolution. The pre-weighed tablet sample is removed after 100 revolutions, dusted and reweighed. Tablets that loose less than 0.5 to 1 percent in weight are generally considered acceptable.

E. Determination of Mucoadhesive Strength: It is important to assess its *in vivo* buccal residence time. In the present study, the mucoadhesive strength of formulated buccoadhesive tablets was evaluated using a modified physical balance.

F. Drug Content Estimation: The Drug content of BenidipineHCl in the prepared buccoadhesive tablets was determined by UV spectrophotometry. From each batch 5 tablets were triturated to form fine powder after knowing the individual weight of each tablet. The powder equivalent to 100 mg of Benidipine HCl was weighed and transferred into a 100 ml

volumetric flask and was dissolved in a mixture of phosphate buffer of pH 6.8 and 3% tween 80.The absorbance of this solution was measured at 239nm by using UV Visible spectrophotometer.

G. Swelling Studies: The tablet was weighed accurately (w1) and placed in Petri dish containing 4 ml of phosphate buffer of ph 6.8. At the end of 2 hours, the tablets were removed from the Petri dish and excess surface water was removed carefully using filter paper and swollen tablets were reweighed (w2). The swelling index was calculated according to the formula:

$$\text{Swelling index (\%)} = [(w2 - w1)/w1] \times 100$$

H. *In-Vitro* Diffusion Studies: The *in-vitro* dissolution study was carriedout in the USP dissolution test apparatus (Lab India Dissolution tester USP)type 2 (paddle). 900 ml of the dissolution medium (phosphate buffer pH 6.8) was taken in vessel and thetemperature was maintained at 37 ± 0.5^0C. Thespeed of the paddle was set at 50 rpm. 5 ml ofthe dissolution medium was withdrawn and thesame amount of fresh medium was replenished o the dissolution medium.And analyzedin the UV spectrophotometer (T-60 Lab India, PG instruments) at 239nm.

4. PREPARATION OF TABLET

Table No: 1. Formulations of Benidipine (F1 to F8).

Ingredients (mg)	F1	F2	F3	F4	F5	F6	F7	F8
BenidipineHCl	4	4	4	4	4	4	4	4
HPMC 6 cps	20	30	20	30	20	30	20	30
Sodium Alginate	20	20	30	-	-	-	-	-
Chitosan	-	-	-	20	30	30	-	-
Carbopol 940	-	-	-	-	-	-	20	20
Lactose	138	128	128	128	128	118	138	128
Mannitol	10	10	10	10	10	10	10	10
Magnesium Stearate	4	4	4	4	4	4	4	4
Talc	4	4	4	4	4	4	4	4
Total Weight (mg)	200	200	200	200	200	200	200	200

5. STANDARD CURVE OF PURE DRUG BENIDIPINE AT PHOSPHATE BUFFER PH 6.8

5.1Preparation of phosphate buffer pH 6.8: About 28.80 g of disodium hydrogen phosphate and 11.45 g of potassium dihydrogen phosphate was weighed accurately and dissolved in sufficient water to produce 1000m

Procedure: Preparation of stock solution: 100 mg of drug was dissolved in 1000 ml of media purified phosphate buffer to give 100 µg/ml. Preparation of dilutions: The different dilutions were made using stock solution prepared. 0.2 ml, 0.4 ml, 0.6 ml, 0.8 ml&1.0 mlof stock solution was taken and made up to 10 ml purified water to get 2, 4, 6, 8, &10 µg/ml concentrations. Absorbance of diluted solutions were taken by using UV – Spectrophotometer at 239 nm wave length, using phosphate buffer as blank.

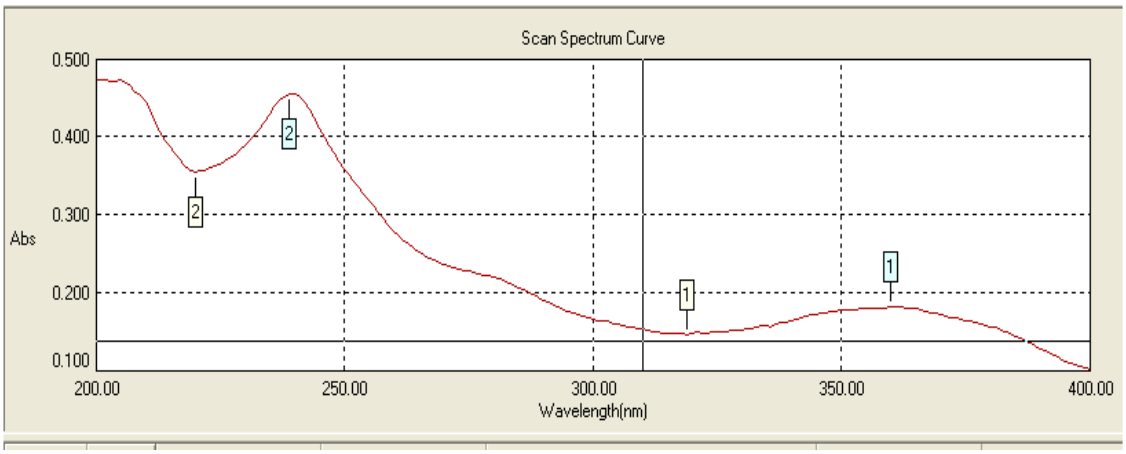


Fig. 9: Determination of λmax.

Absorption maximum: uv max 239 nm

COMPATIBILITY STUDY BY FT-IR

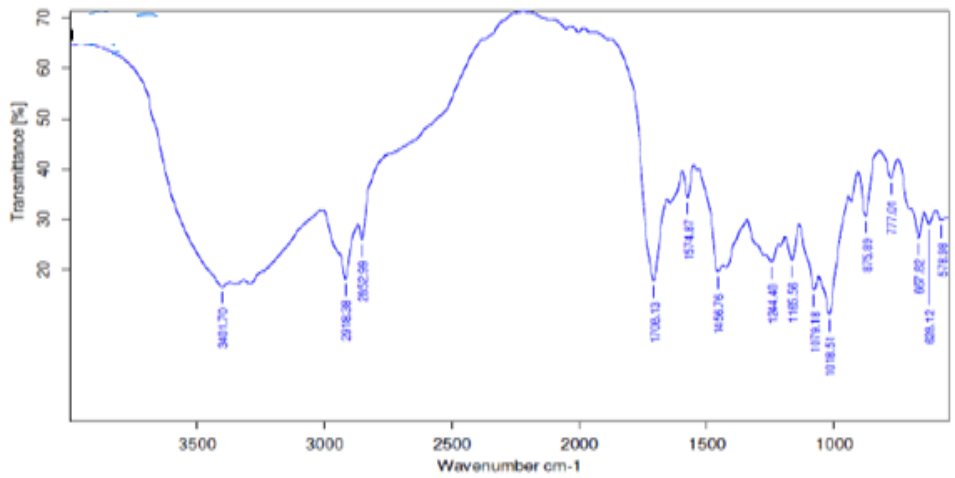


Fig. 10: FTIR spectra of Pure drug.

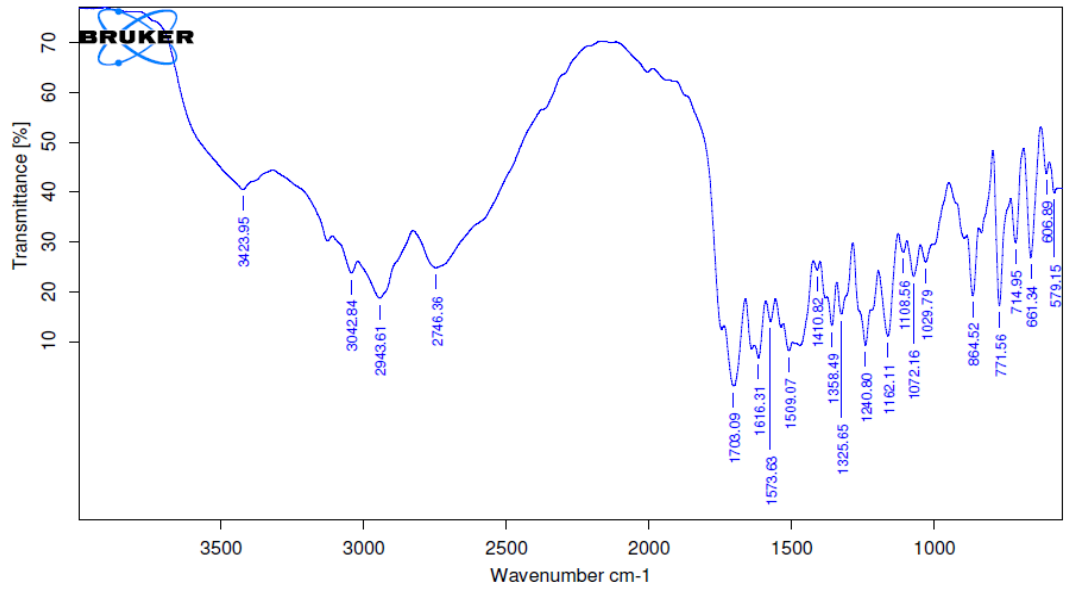


Fig. 11: FT-IR spectra of Benidipine HCl and Carbopol 940.

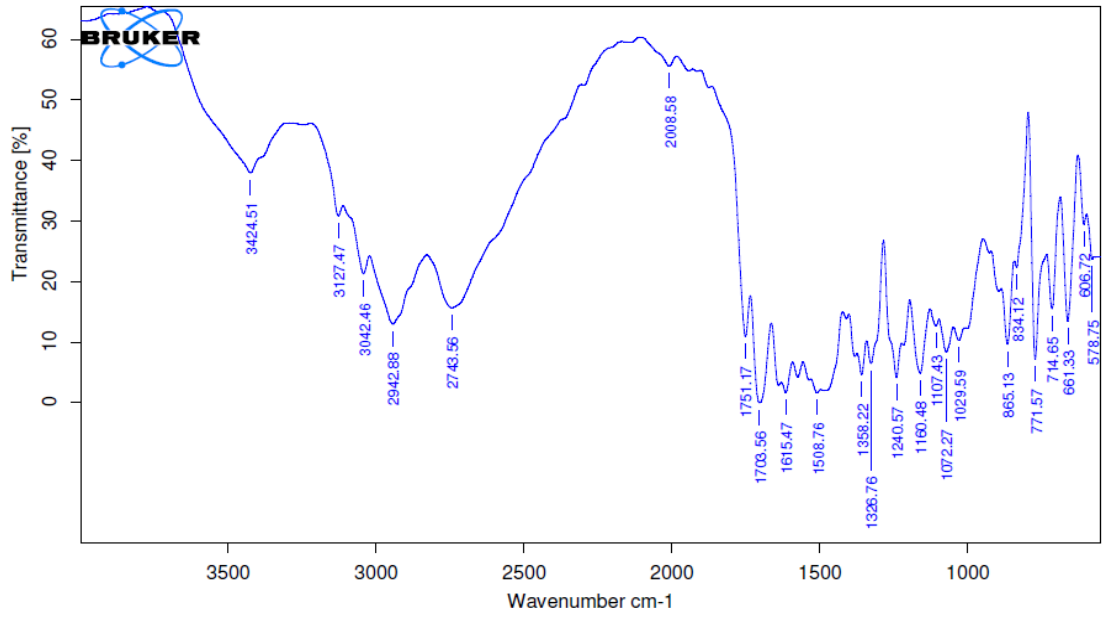


Fig. 12: FT-IR spectra of Benidipine HCl and HPMC.

From the FTIR spectra of pure drug and drug-excipient mixture it was found that drug and excipients were compatible with each other as there was no interference of peaks or existence of extra prominent peaks. Peaks of spectrum of pure drug were compared with the peaks of the spectra of physical mixtures of drug and polymers. It was observed that characteristic IR absorptionpeaks of Benidipine HCl were not altered in physical mixture without any change in their position. This ruled out the drug-polymers interaction indicating the drug is compatible and stable in the formulation.

5.2 Construction of Calibration Curve for Drug at λ_{max} 239nm

Procedure: 100 mg of drug is taken in a 100 ml volumetric flask and dissolved with 10 ml of methanol, after complete dissolution, make up the volume upto 100 ml with pH 6.8 phophate buffer to get 1000µg/ml as a stock solution-1, from this prepared 100µg/ml as a stock solution-2.

From stock solution-2, 10µg/ml concentration is prepared and sujected for scan 400-200 nm in UV-Visible spectrophoto meter and maximum absorbance obseved at 239 nm (**λ max**).

Construction of Standard graph at phosphate buffer pH 6.8

From stock solution-2, 1-10 µg/ml concentration solutions were prepared and subjected for absorbance at 239 (**λ max)**

Table 10: Standard Calibration graph.

S.No	Con (µg/ml)	Absorbance at 239 nm
1	0	0.000
2	2	0.096
3	4	0.181
4	6	0.276
5	8	0.363
6	10	0.457

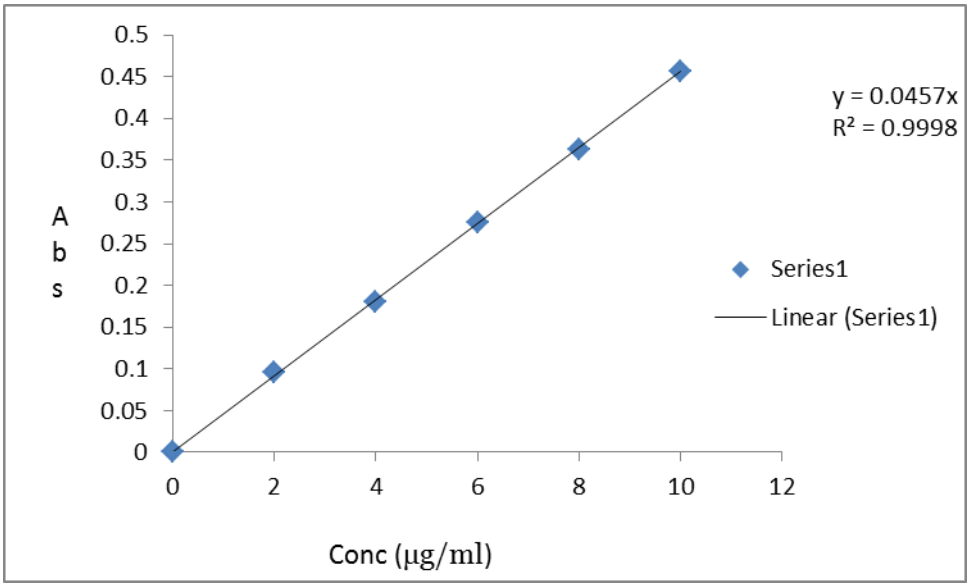


Fig 13: standard calibration curve.

Table 11: Evaluation of physicochemical properties of Benedipin.

Physiochemical evauation of Benedipine. Formulation Code	Bulk density (mg/ml)	Tapped density(mg/ml)	Compressibility index (I)	Hauser's ratio
F1	0.43	0.48	10.41	1.11
F2	0.46	0.52	11.53	1.13
F3	0.42	0.48	12.50	1.14
F4	0.38	0.45	15.55	1.18
F5	0.46	0.56	14.28	1.16
F6	0.48	0.55	12.72	1.14
F7	0.39	0.43	11.30	1.10
F8	0.45	0.51	11.76	1.13

Table 12: Evaluation of Tablets.

S. No	Evaluation								
		F1	F2	F3	F4	F5	F6	F7	F8
1	Average weight (mg)	200.5 ±0.20	200.7 ±0.19	200.8 ±0.35	200.8 ±0.16	199.5 ±0.30	200.1 ±0.29	200.8 ±0.25	200.5 ±0.16
2	Average Thickness(mm)	2.89 ±0.03	2.81 ±0.01	2.81 ±0.02	2.85 ±0.03	2.85 ±0.04	2.88 ±0.02	2.89 ±0.05	2.85 ±0.02
3	Hardness (Kg/ cm^2)	3.1	3.3	3.6	3.7	3.0	3.3	3.2	3.1
4	Friability (%)	0.149 ±0.01	0.145 ±0.02	0.135 ±0.03	0.139 ±0.03	0.145 ±0.02	0.148 ±0.02	0.133 ±0.04	0.135 ±0.03
5	Mucoadhesive strength (g)	7.75 ±0.53	11.29 ±0.25	13.99 ±0.23	15.40 ±0.18	7.70 ±0.23	10.25 ±0.20	12.80 ±0.23	12.45 ±0.15
6	Drug content (%)	96.84 ±0.46	97.98 ±0.66	98.62 ±0.64	97.26 ±0.98	97.44 ±0.42	98.78 ±0.46	98.98 ±0.60	97.47 ±0.56
7	Swelling index (%)	78.61 ±2.05	80.64 ±0.63	86.67 ±1.26	88.72 ±1.83	88.64 ±2.47	85.64 ±0.75	88.60 ±1.45	88.72 ±1.05

DISSOLUTION OF BENIDIPINE HYDROCHLORIDE BUCCAL TABLETS

Drug release profiles of Marketed Product(CARITEC) and F1, F2, F3, F4Formulations

Table 13: Drug release profile of marketed product, F1, F2, F3, F4.

Time (hrs)	Marketed product % drug Release	F1 Cumulative % drug release	F2 Cumulative % drug Release	F3 Cumulative % drug Release	F4 Cumulative % drug Release
0	0	0	0	0	0
2	13.5	42.72	49.13	23.93	30.78
4	65.5	63.15	68.52	47.73	52.36
6	78.4	84.72	88.34	67.34	76.92
8	89.68	94.85	96.58	86.26	87.48
10	96.58	-	-	96.30	99.50
12	-	-	-	-	-

The above figure shows the in-vitro release profiles of Benidipine HCl buccal tablets of formulations F1, F2, F3, and F4. Effect of polymer on the release profile of Benidipine HCl was studied. In formulation F1, F2 and F3, F4 different concentrations of Benidipine HCl were used. The release of the drug from the tablet was release up to 94.85% for F1 and 96.58% for F2 in 8 hours. And for F3 and F4 was 96.30% and 99.50%. In 10 hours only, so the polymer is not having the capacity to extend the release up to 12 hours.

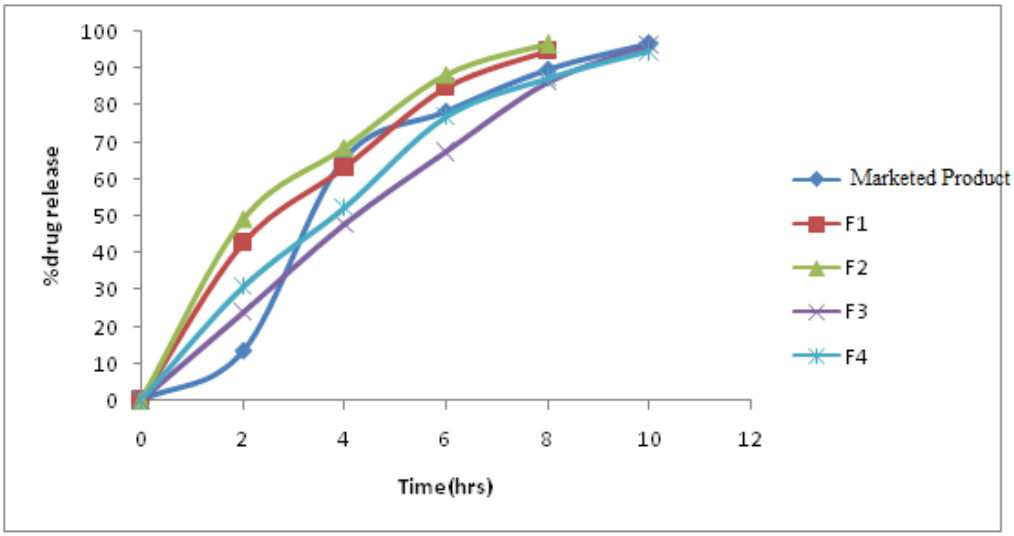


Fig 13: Drug release profile of innovator and F1, F2, F3, F4 Formulations.

Drug release profiles of F5, F6, F7, F8, Formulations

Table 14: Drug release profile of Marketed tablet, F5, F6, F7& F8.

Time (hrs)	Marketed % drug Release	F5 Cumulative % drug Release	F6 Cumulative % drug release	F7 Cumulative % drug Release	F8 Cumulative % drug Release
0	0	0	0	0	0
2	13.5	32.72	35.67	20.96	17.85
4	65.5	51.87	51.87	47.20	42.72
6	78.4	73.24	73.24	65.60	63.15
8	89.68	88.69	89.59	71.20	78.12
10	96.58	98.26	97.68	94.90	92.58
12	-	-	-	98.9	93.78

The above figure shows the *In vitro* release profiles of Benidipine HCl buccal tablets of formulations F5, F6, F7, F8 effect of polymers on the release profile of Benidipine HCl was studied. The formulation F7, F8 showed 98.9% and 93.78% respectively for 12hr. The formulation F7 showed 98.9% up to 12hrs.

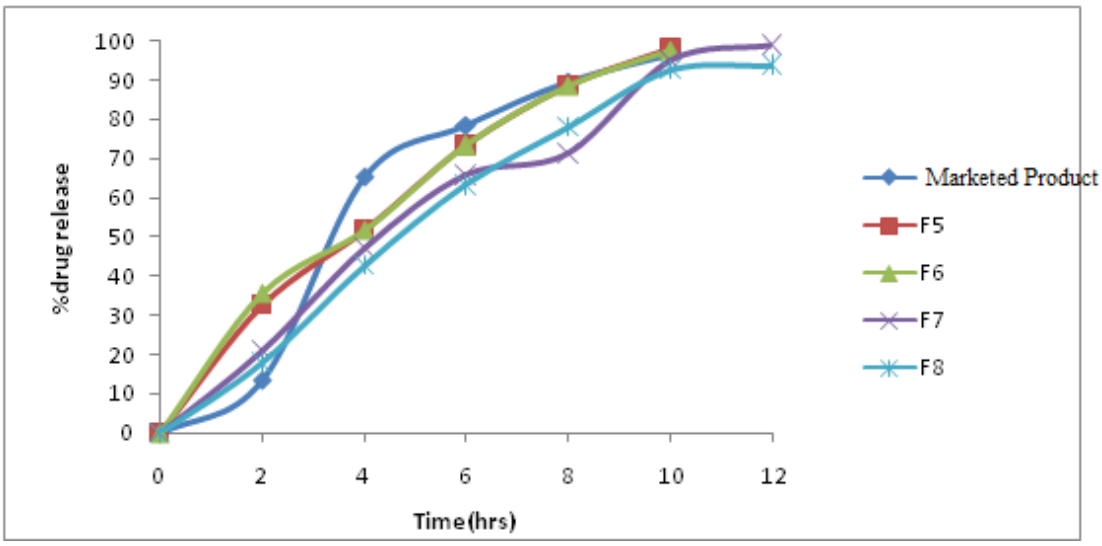


Fig: 14 Drug release profile of marketed product(CARITEC) and F5, F6, F7, F8.

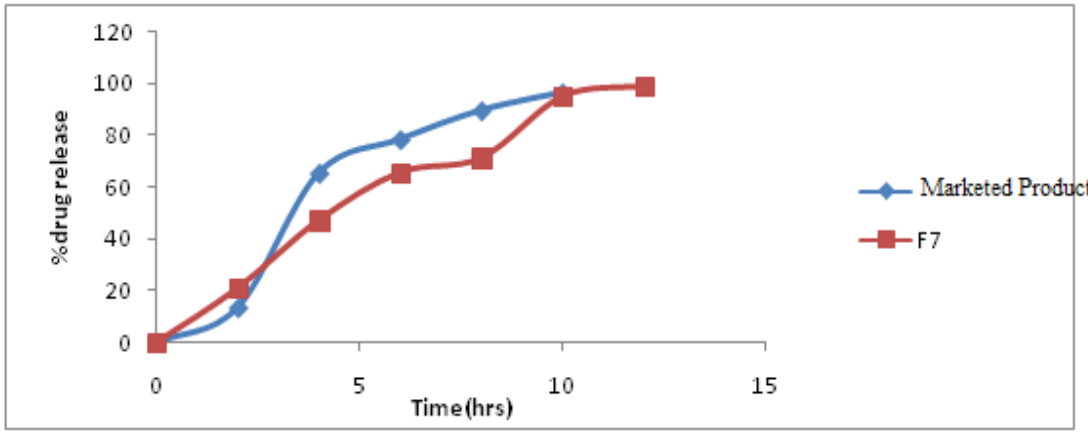


Fig. 15: Drug release profile of marketed product(CARITEC) and Optimized (F7) Formulation.

DISCUSSION

The above figure shows the *In vitro* release profiles of optimised Benidipine HCl buccal tablet formulation(F7)and Marketed product (CARITEC) was studied. The formulation F7 showed 98.9% drug release in 12 hours and marketed product (CARITEC) showed 99.8% drug release in 10 hrs.

SUMMARY

The purpose of the present study was formulation development and evaluation of Benidipine HCl buccal tablets of strength 4 mg. Direct compression technique was chosen to develop a finished pharmaceutical product. Various formulations (F1-F8) were taken. In these trials, drug: excipient ratio was varied and the effect of diluents, and various polymers like, HPMC

15 cps as a rate controlling polymer, and Sodium Alginate, Chitosan, Carbopol 940 are as mucoadhesive polymers on the performance tablets was studied. All the formulation has hausner's ratio between the 1.10 to1.18. It indicates all the formulation show better flow property. The physical parameters like weight variation, hardness, thickness, drug content of the prepared tablets were within the pharmacopoeial limits. The total weight of each formulation was maintained constant. The weight variation of tablets was within the limit of 7.5% as specified. , Hardness ranges 3.0 to 3.7 kg/cm^2 and the friability loss of less than 1% in weight is generally acceptable. Content uniformity 96.84% to 98.98 %, Mucoadhesive Strength 7.70 to 15.40 and Swelling index is 78.61 to 88.72% was found. Among all formulation F7 showed in-vitro drug release 98.9% for 12hrs. And which is showed better release than marketed preparation hence considered as most promising preparation.

CONCLUSION

The Benidipine HCl buccal tablets were prepared by direct compression method. The nature of the polymer influences the physical and release characteristics of the buccal tablet. Sodium Alginate, Chitosan, Carbopol 940 are used as mucoadhesive polymers. The hydrophilic polymer, HPMC (15 cps) has controlled the release of drug. Among all formulations (F1 – F8), F7 containing Carbopol 940 with HPMC 15 cps, showed better mucoadhesive strength (12.80 g) and release of drug (98.9%) from buccal tablet for 12 hours was observed.

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