DEVELOPMENT AND CHARACTERIZATION OF CILNIDIPINE BUCCAL TABLETS IN QUALITY BY DESIGN FRAMEWORK

K. Mahallingan*[1], Vedamurthy Joshi[2]

[1]Research Scholar, Department of Pharmaceutics, Adichunchanagiri University, B.G. Nagara and Associate Professor, RR College of Pharmacy, Bangalore, Karnataka, India.

[2]Department of Pharmaceutics, Sri Adichunchanagiri College of Pharmacy, B.G. Nagara, Karnataka, India.

ABSTRACT

In the present study mucoadhesive buccal tablets of Cilnidipine were developed by using mucoadhesive polymers for the treatment of hypertension. Nine formulations were prepared by using DoE method called Extreme Vertices Mixture Design. Hardness (kg/cm^2) and drug release at 12 hr (%) were considered in the design as dependent variables for the development of Cilnidipine buccal tablets and the independent variables factored in the design were HPMC K4M, HPMC K15M and Carbopol 934. Pre compression studies like angle of repose, bulk density, tapped density, Hausner's ratio and Carr's index were studied for powder blends and the values shows that the granules having good flow properties and compression characteristics. Post compression studies such as weight variation, thickness, hardness, friability, content uniformity, swelling index, surface pH, bioadhesive strength, *in vitro* dissolution, and stability studies were carried out. BTF9 formulation was selected as best formulation based on physico chemical parameters and *in-vitro* dissolution and diffusion values. Stability studies for the best selected formulation showed no significance changes in the parameters such as hardness, drug content, i*n-vitro* dissolution and diffusion studies. Therefore, the buccal tablets of Cilnidipine can be developed successfully by using mucoadhesive polymer for the treatment of hypertension.

Key words: Mucoadhsive drug delivery system, buccal tablets, Cilnidipine, mucoadhesive strength, *in-vitro* dissolution study

Corresponding author

*****K. Mahalingan, Research Scholar, Department of Pharmaceutics, Adichunchanagiri University, B.G. Nagara and Associate Professor, RR College of Pharmacy, Bangalore, Karnataka, India. Mobile No.: 9886079504, Email: kmahalingan@gmail.com,

INTRODUCTION

Mucoadhesive drug delivery systems utilize the property of bioadhesion of certain polymers which became adhesive on hydration, hence, can be used to target the drug to a particular part of the body for extended period of time [1]. The transmucosal delivery of drug can involve the mucosal lining of buccal, sublingual, nasal, vaginal, rectal and ocular. Among that oral mucosa is perhaps most convenient and preferred route for drug delivery [2]. For this reason, several buccal formulations like mucoadhesive tablets [3 - 5], patches, and buccal films [6 - 12] gels [13 - 15], disks [16 - 17], strips [18] and ointment [19] have been developed using polymers that allow the most direct contact with the mucosa and provide a prolonged release of the drug, reducing the need for administration of repeated doses [7, 20].

Drug administration through the mucosal membranes lining the cheeks and gums are oral mucoadhesive drug delivery systems. Buccal drug delivery system offers number of advantages such as drug directly delivered to systemic circulation and avoiding degradation by gastro-intestional enzymes, first pass hepatic metabolism, mucosa of buccal is reach in blood supply with good permeability of drugs and it has great appeal for both local as well as systemic drug bioavailability, provides rapid drug transport to the systemic circulation and low patient compliance [21]. It is easily accessible for self medication and the administered drug can be terminated by removing the dosage form from buccal cavity in case of toxicity [22].

METHODOLOGY

Development of Cilnidipine buccal tablets in Quality by Design (QbD) framework

Defining Quality Target Product Profile (QTTP) and Critical Quality Attributes (CQAs)

QTPP is an essential element of QbD defined as "A prospective summary of quality characteristics of a product that ideally to be achieved to ensure desired quality into the product by considering safety and efficacy of the product" (ICH Q8 Reference). The design criteria for the product development essentially provided by the QTPP. Based on the functional attributes of the mucoadhesive drug delivery systems and also based on the literature review, QTPPs were defined in table 1. The product attributes defining the QTPP for mucoadhesive drug delivery systems includes hardness and % drug release. The Critical quality attributes of mucoadhesive formulations with proper justification has been illustrated in the table 2.

Table 1: QTPP for Cilnidipine mucoadhesive buccal tablets formulations

QTPP Elements	Target	Justification
Dosage type	Mucoadhesive drug delivery	Bioavailability improvement
Dosage form	Tablets	Ease of administration
Dosage strength	10 mg	Target dose of 10 mg
Route of administration	Buccal	Convenient route
Pharmacokinetics	Tmax, Cmax, AUC	To understand and estimate the extent of bioavailability of the attempted formulation
Stability	As per the conditions of ICH Q1B Long term stability studies	To assess degradatory pattern of the Drug and excipients used in the formulation.

Table 2: CQAs of Cilnidipine buccal tablets formulations and their justification

Quality Attributes of product		Target	CQA	Justification
Physical attributes	Color	Acceptable to patient	No	The physical attributes were not directly related to the efficacy and safety of the product
	Odor			
	Appearance			
Hardness (kg/cm^2)		4 to 7	Yes	Has direct correlation with bioavailability
Drug content (mg)		10 mg per dose	Yes	10 mg per unit dose essential
Drug release at 6 hrs		65 to76 %	Yes	Has direct correlation with bioavailability

Mixture design: Development and optimization of Cilnidipine buccal tablets was done by using a Design of experiments (DoE) method called Mixture design-Extreme Vertices Mixture Design (EVMD) was used (Cleland D and Mccluskey A. 2013). Since EVMD is a constrained mixture design, the factors are the mixture components subjected to constraints such as low and high level for each factor and the components or the factors expressed as fractions which sum to one or 100% (Snee D and Marquardt DW. 1974). For the development of Cilnidipine buccal tablets, the responses or the dependent variables considered in the design are Hardness (kg/cm^2) and *in*

vitro drug release (%) at 12 hr. The independent variables factors in the EVMD design were HPMC K4M, HPMC K15M and Cabopol 934. Factors with the constraints and the responses considered in the EVMD are presented in the table 3 and 4.

Table 3: Composition and limits of experimental domain

Factors	Role	Values	
		Low	High
HPMC K4M (mg)	Mucoadhesive polymer	30	90
HPMC K15M (mg)	Mucoadhesive polymer	30	90
Carbopol 934 (mg)	Mucoadhesive polymer	30	90

Table 4: Responses in mixture design

Responses	Goal	Lower limit	Upper limit
Hardness (kg/cm^2)	Maximize	4.13	5.61
Drug release at 12 hr (%)	Maximize	88.79	92.2

Least Squares Fit: Response Hardness and Response % CDR at 12 hrs

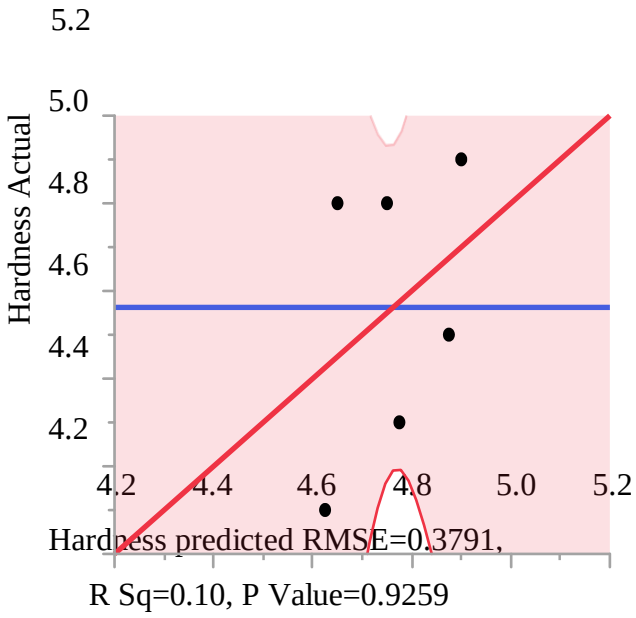

Fig 1: Least Squares Fit: Response Hardness

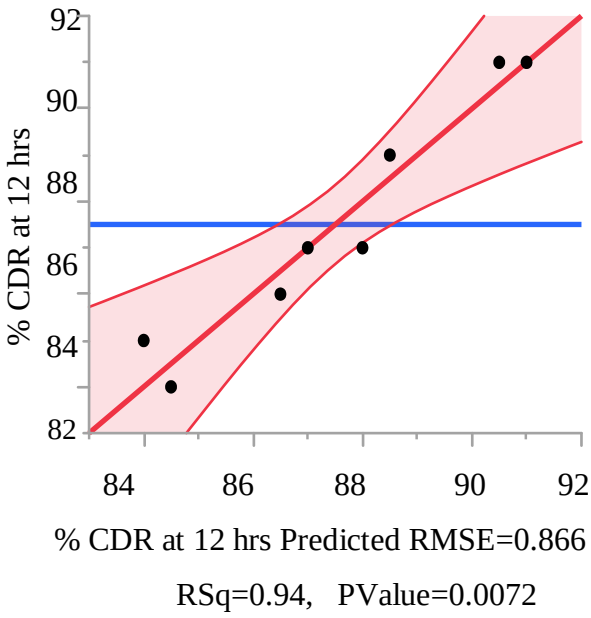

Fig 2: Least Squares Fit: Response % CDR at 12 hrs

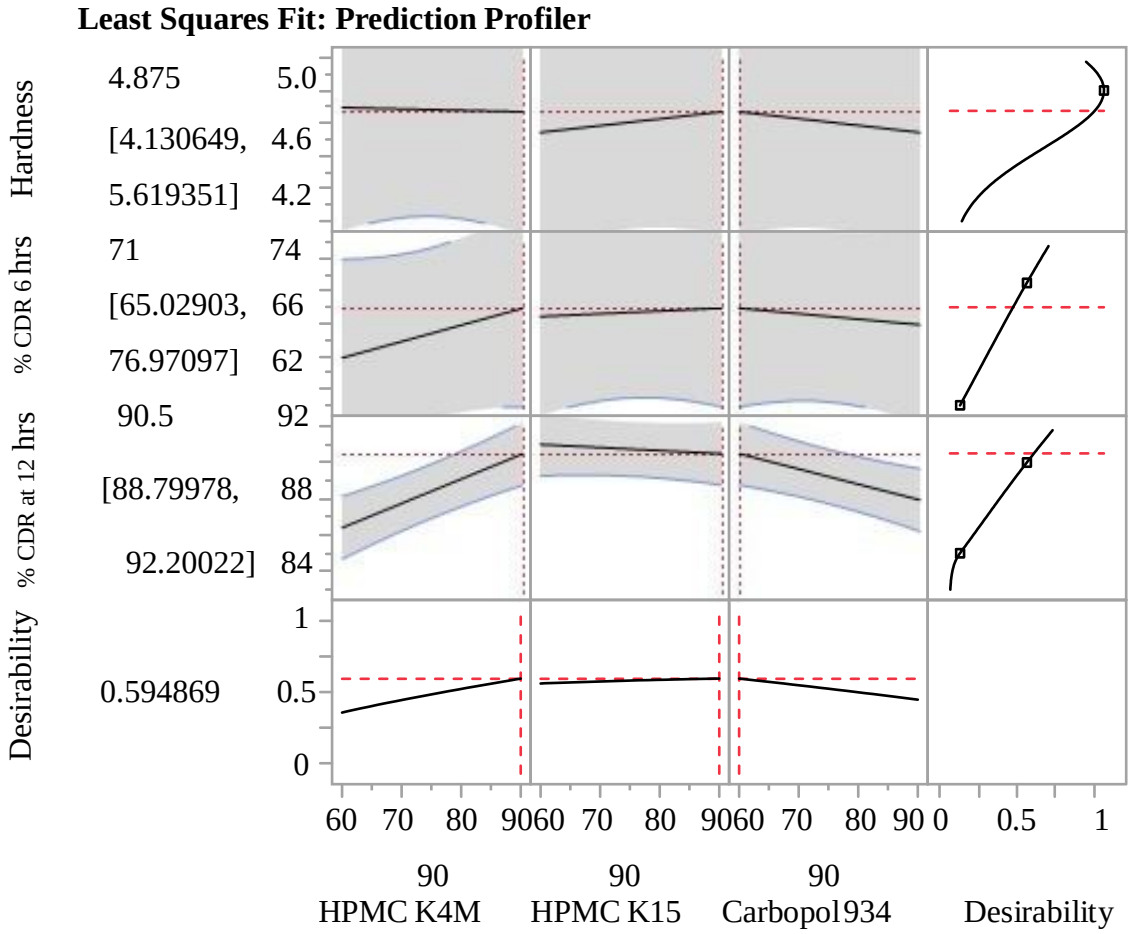

Fig 3: Least Squares Fit: Prediction Profiler

Preparation of Buccal tablets

Buccal tablets of Cilnidipine were prepared by direct compression method by using mucoadhesive polymers such as HPMC K4M, HPMC K15 and Carbopol 934 as mucoadhesive polymers. Drug, polymer and excipients were blended in the ascending order for 10 min. Then, lubricant and glidents were added and mixed again for two min. After uniform mixing, the blend was compressed in to tablets using 12 stations Remi tablet punching machine with low compression force to form single layered flat faced tablet. 50 mg of ethyl cellulose was used as backing layer and final compression was done with high compression force.

Pre compression studies [23].

Angle of repose (θ): A glass funnel was placed with a clamp and a graph paper was kept below the paper. 10 g of powder blend was poured in to the funnel keeping the orifice covered by

thumb to maintain the gap of 6.4 mm between the bottom of the funnel stem and the top of the power pile. The procedure was repeated to measure the height of the heap, diameter and radius.

$$\text{Angle of repose } (\theta) = \tan^{-1} (h/r)$$

Where,

θ = angle of repose, h = height of the heap of the powder, r = radius of the powder

Bulk density and Tapped density: Initial volume of powder blend (W) was measured by adding 20 g of powder blend in a 100 ml of measuring cylinder. 100 tapping were entered and the cylinder was allowed to tap for 100 times. After tapping, the volume of measuring cylinder was noted and the bulk density and tapped density were calculated using the formula.

$$\text{Bulk density} = W/V_O \text{ and Tapped density} = W/V_F$$

Where,

W = Weight of the initial granules, V_O = Initial volume, V_F = Final volume.

Hausner's Ratio: It was done to find the flow properties of the powder blend and it is measured by the ratio of tapped density and the bulk density.

$$\text{Hausner'r ratio} = \text{Tapped density/Bulk density}$$

Compressibility Index: It is done to determine the flow ability of powder blend and can be calculated by comparing the bulk density and tapped density of powder mixture.

$$\text{Carr's Index (\%)} = \frac{\text{(Tapped density - Bulk density)}}{\text{Tapped density}} \times 100$$

Post compression studies [23, 24]

Appearance: The prepared buccal tablets were selected randomly from each formulation and checked for the defects.

Weight variation: Twenty tablets were randomly selected from each formulation and weighed individually. The average weight was calculated by adding the weight of individual tablet and divided by twenty. Deviation in weight and % variation of each tablet was calculated by individual tablet weight was compared with the average value.

Hardness: Hardness of ten randomly selected tablets from each formulation was measured by using Monsanto hardness tester to find the strength of the prepared tablets.

Thickness: From each formulation, three tablets were randomly selected and the thickness was measured by using Vernier Calliper.

Friability: Pre weighed 20 tablets was placed in a friabilator chamber revolving up to 100 revolutions by dropping tablets at height of 6 inch and the tablets were reweighed.

% Friability = [(Initial weight – Final weight) / Initial weight] x 100.

Content uniformity: Randomly selected 5 tablets were powered from the each formulation and the quantity of the powder equivalent to dose of the drug was accurately weighed and transferred in to 100 ml volumetric flask. 50 ml of 0.1 N HCl solution was added to dissolve the powder and the volume was made upto 100ml with the same solution. The solution was filtered through whatmann filter paper and 5 ml of the filtrate was diluted to 100 ml with the same buffer solution and analyzed using U.V Spectrophotometer to determine drug concentration.

Surface pH: One tablet from each formulation was kept in contact with 5 ml of phosphate buffer pH 6.8 for 2 hrs at room temperature. The pH of the tablet was measured by bringing the electrode in contact with the surface of the tablet.

Mucoadhesion strength and Residence Time: It was determined by using a modified balance method. Sheep buccal mucosa was collected and underlying fat and loose tissues were removed. The mucosal membrane was washed with distilled water and phosphate buffer pH 6.8 and then cut in to pieces and attached to the flat end of beaker with the help of adhesive. A watch glass attached to thin chains at equal distance forms the left hand pan and the tablet was adhered above the mucosa to the lower side of the watch glass. In right pan an empty beaker was kept and both the pans are balanced by addition of weights. 5 g weight was removed from right pan, which lowered the left pan results tablet to come in contact with mucosa and the balance was allowed in this position for 3 min. Water was added gradually to the right pan until tablet detaches from the buccal mucosa and weight requires to detach the tablet from the buccal mucosa was noted [25].

***In-vitro* dissolution studies:** USP dissolution apparatus-II was used to study the *in-vitro* drug release. Paddle was stirred at 50 rpm and 900 ml of dissolution medium was used and maintained at 37 ± 0.5°C. One side of tablet was fixed to a glass slide with adhesive to release the drug from one side and the slide side was placed at the bottom of the vessel. 5 ml sample was withdrawn at predetermined time intervals and same volume of fresh dissolution medium was replaced. Samples were filtered through whatmann filter paper and 1 ml of solution was taken and diluted to 10 ml with medium and analyzed using UV spectrophotometer.

K**inetics studies:** *In vitro* drug release data of formulation BTF9 was fitted in to Zero order, First order, Higuchi's and Korsmeyer Peppas equations for determination of release kinetics and release mechanism.

Stability studies: Stability studies were carried out for the best formulation BTF9 as per ICH guidelines. Tablets were kept in the aluminium packaging under the conditions at 40 ± 2°C & 75 ± 5 % RH in stability chamber. After one, three and six month period, studies like hardness, drug content, swelling index and *in-vitro* dissolution were carried out.

RESULTS AND DISCUSSION

Angle of repose: Angle of repose of the powder mixture was in the range of 23.8° to 26.7° and the results indicating that excellent flow property of the powder blend.

Bulk density and Tapped density: Bulk density values were found to be 055 to 0.68 g/cc and tapped density values were found to be 0.58 to 0.72 g/cc and the values were within the limit.

Hausner's ratio: Hausner's ratio values were found in the range of 1.07 to 1.14 indicates good flow properties of powder blend.

Carr's index: Carr's index values were in the range of 10.19 to 11.13 % which indicates that granules of all the formulations have good flow properties and powder bed is compressible.

Weight Variation: All the formulations were evaluated for their uniformity of weight and the minimum weight was 198 ± 0.39 mg and the maximum weight was 203 ± 0.35 mg. Results indicate all formulations were complying with the standards.

Hardness: Average hardness values were found to be between 4.1 ± 0.41 to 5.5 ± 0.67 kg / cm^2 and values are within the range.

Thickness: Thickness was measured by using Vernier calliper and the ranges were found to be 2.7 ± 0.63 mm to 3.1 ± 0.52 mm. The average thickness of all the formulations was within the allowed limit.

Friability: All the formulations were evaluated for their percentage friability and the average % friability was in the range of 0.15 % to 0.75 %, which was considered acceptable.

Content uniformity: Content uniformity of all the formulations were observed in the range of 95.90 ± 0.47 % to 98.31 ± 0.45 % and the results shows that all the formulations contain amount of drug were within 10 % deviation.

Surface PH: All the prepared tablets were subjected for surface pH and the values are between 6.14 ± 0.39 to 7.12 ± 0.34, which is in the range of salivary pH of 6.0 to 7.4. Hence, it may not produce any irritation to the buccal mucosa.

Swelling index: Swelling index of all the formulations showed gradual increase in swelling with time and are in the range of 56.0 % to 92.5 %. The swelling index increased with time and concentration of polymers increases.

Mucoadhesive Strength and Residence Time: Mucoadhesive strength of all the formulation were found to between 28.65 g to 36.14 g and Residence time was found to be 4.5 hrs to 6.7 hrs. An increase in the polymer concentration was associated with decrease in permeation rate of the drug. Since, increasing the amount of polymer forms a water-swollen gel-like state that could considerably reduce the penetration of medium into the tablet then the drug release was retarded.

***In vitro* dissolution studies:** The results of *in-vitro* drug release are plotted in to a graph by time versus % CDR, represented in the figure 4. The graph indicates that the time of drug release varies from 6 hrs to 12 hrs, because the concentration of polymer increases, the drug release decreases and prolong the drug release.

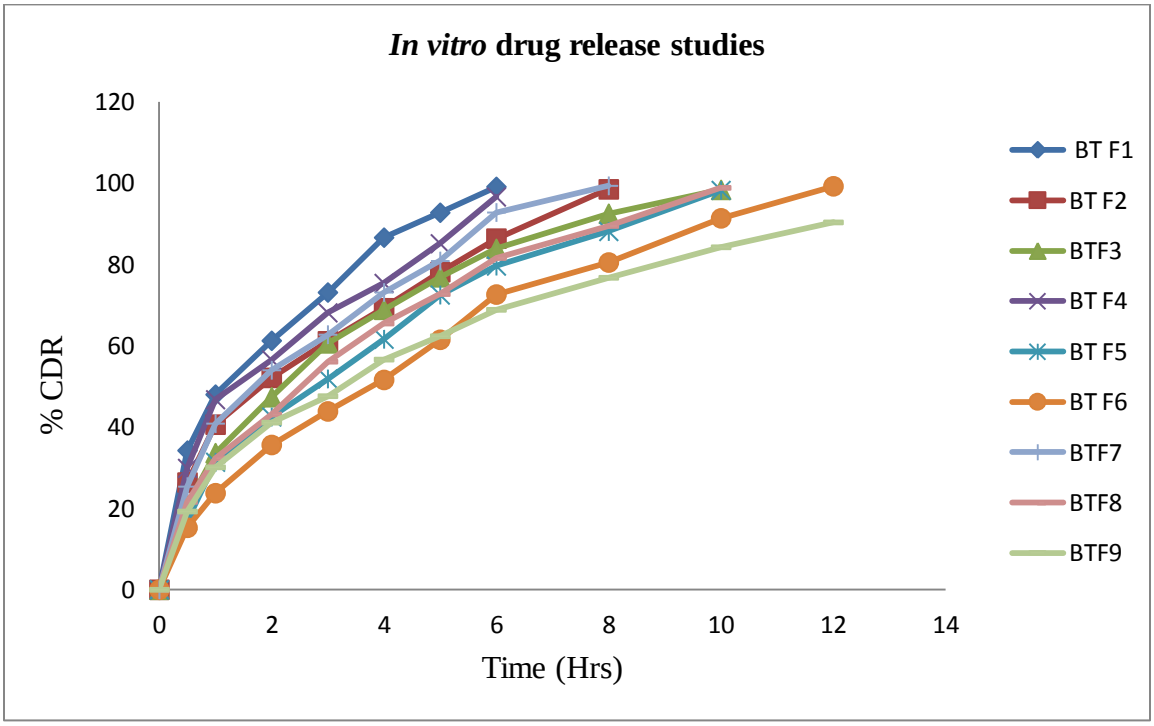

Fig 4: *In vitro* drug release study

Kinetics studies: *In vitro* drug release data of selected formulation BTF9 was fit into various kinetics models. The plots were found linear in case of Higuchi kinetics with r^2 values nearer to 1 ($r^2 = 0.994$) and the slope values of the Peppas equation are less than 1 (n = 0.477) indicating that the drug release mechanism was diffusion controlled with Fickian release were represented in table 5.

Table 5: Kinetics modeling data

Formulation Code	Drug release kinetics		Mechanism of drug release		
	Zero order	First order	Higuchi model	Korsmeyer Peppas model	
	Correlation coefficient (r^2)	Correlation coefficient (r^2)	Correlation coefficient (r^2)	Correlation coefficient (r^2)	Slope 'n' value
BTF9	0.936	0.795	0.995	0.994	0.477

Stability studies: The results of stability studies shows that there is no significance change in the hardness, drug content, swelling index and *in-vitro* dissolution after one, three and six month period indicates that the formulation BTF9 was stable revealing low risk of the product failure.

CONCLUSION

Development of mucoadhesive buccal tablets of Cilnidipine using different mucoadhesive polymers such as HPMC K4M, HPMCK15M and Carbopol 934 in different concentration were successfully prepared and labelled as BTF1 to BTF9. The prepared tablets were evaluated for preformulation studies and post formulation studies. Formulation BTF9 was selected as best formulation based on physicochemical and *in vitro* dissolution studies. *In vitro* data of BTF9 was fit into various kinetics models and found linear in case of Higuchi kinetics with $r^2 = 0.994$ and the n values of the Peppas equation are less n= 0.477 shows that the mechanism of drug release was diffusion controlled with Fickian release. The stability studies were carried out for formulation BTF9 and there were no significance change in the hardness, surface pH, swelling index drug content and *in vitro* dissolution studies. Hence, Cilnidipine buccal tablets can be used to improve the drug bioavailability and patient compliance.

REFERENCE

1. Khanna R., Agraval S.P., Ahuja A. Mucoadhesive buccal drug delivery a potential alternative to conventional therapy. Ind. J. pharma. sci. 1998; 60 (1):1-11.
2. Kamath K.R., Park K., Swarbrick J. and Boylan J.C. Eds, Encyclopedia of pharmaceutical technology, 1994.vol 10, Marcel Dekker, New York.
3. B. Parodi, E. Russo, P. Gatti, S. Cafaggi, and G. Bignardi. Development and in vitro evaluation of buccoadhesive tablets using a new model substrate for bioadhesion measures: the eggshell membrane; Drug Development and Industrial Pharmacy, 1999. 25(3):289-95.
4. S. Mohammadi-Samani, R. Bahri-Najafi, and G. Yousefi. Formulation and in vitro evaluation of prednisolone buccoadhesive tablets; Farmaco, 2005. 60(4). 339-44.
5. Y. Ikeuchi-Takahashi, M. Sasatsu, and H. Onishi. Evaluation of matrix type mucoadhesive tablets containing indomethacin for buccal application, International Journal of Pharmaceutics, 2013. 453(2): 454-61.
6. R. M. Obaidat, A. Bader, W. al-Rajab, G. Abu Sheikha, and A. A. Obaidat, Preparation of mucoadhesive oral patches containing tetracycline hydrochloride and carvacrol for treatment of local mouth bacterial infections and candidiasis, Scientia Pharmaceutica, 2011. 79(1):197-212.
7. A. Abruzzo, F. Bigucci, T. Cerchiara, F. Cruciani, B. Vitali, and B. Luppi, Mucoadhesive chitosan/gelatin films for buccal delivery of propranolol hydrochloride, Carbohydrate Polymers, 2012. 87(1) 581-88.
8. J. O. Morales and J. T. McConville, Manufacture and characterization of mucoadhesive buccal films, European Journal of Pharmaceutics and Biopharmaceutics, 2011. 77(2):187-99.
9. S. Singh, S. Jain, M. S. Muthu, S. Tiwari, and R. Tilak, Preparation and evaluation of buccal bioadhesive films containing clotrimazole, AAPS PharmSciTech, 2008. 9(2): 660-67.
10. S. Yehia, O. el-Gazayerly, and E. Basalious, Fluconazole mucoadhesive buccal films: in vitro/in vivo performance, Current Drug Delivery, 2009. 6(1): 17–27.
11. C. Cavallari, A. Fini, and F. Ospitali, Mucoadhesive multiparticulate patch for the intrabuccal controlled delivery of lidocaine, European Journal of Pharmaceutics and Biopharmaceutics, 2013. 83(3): 405-14.
12. M. Jug, I. Kosalec, F. Maestrelli, and P. Mura, Development of low methoxy amidated pectin-based mucoadhesive patches for buccal delivery of triclosan: effect of cyclodextrin complexation, Carbohydrate Polymers, 2012. 90(4): 1794-1803.

13. V. K. Rai, N. P. Yadav, P. Sinha et al., Development of cellulosic polymer based gel of novel ternary mixture of miconazole nitrate for buccal delivery, Carbohydrate Polymers, 2014.10(3): 126–133.
14. J. Xu, S. Strandman, J. X. X. Zhu, J. Barralet, and M. Cerruti, Genipin-crosslinked catechol-chitosan mucoadhesive hydrogels for buccal drug delivery, Biomaterials, 2015. 37: 395–404.
15. Ana Camila Marques et al., Development and characterization of mucoadhesive buccal gels containing lipid nanoparticles of ibuprofen, Int J Pharm. 2017. 533(2):455-62.
16. Rough-Yee Han et al., Mucoadhesive buccal disks for novel nalbuphine prodrug controlled delivery: effect of formulation variables on drug release and mucoadhesive performance, Int J Pharm. 1999, 177(2), 201-9.
17. Soad A Yehia et al., Design and In Vitro/In Vivo Evaluation of Novel Mucoadhesive Buccal Discs of an Antifungal Drug: Relationship between Swelling, Erosion, and Drug Release. AAPS Pharm Sci Tech; 2009. 9(4):1207-17
18. Nayla Francine Garcia Pastório et al., Design of Mucoadhesive Strips for Buccal Fast Release of Tramadol. Pharmaceutics. 2021.13(8):1187.
19. Milan Petelin et al., EPR study of mucoadhesive ointments for delivery of liposomes into the oral mucosa; Int J Pharm. 1998; 17(3):193-202.
20. V. Sankar, V. Hearnden, K. Hull et al., Local drug delivery for oral mucosal diseases: challenges and opportunities, Oral Diseases. 2011; 17(1); 73-84.
21. Suresh P Kumar et.al. Formulation and evaluation of Nebivolol mucoadhesive buccal tablet. Pharmacology online. 2011; 3: 869-85.
22. S. Velmurugan et.al. Formulation and *in-vitro* Evaluation of Buccal Tablets of Piroxicam. Int J. Pharm Tech Res. 2010; 2(3); 1958-68.
23. Subrahmanyam CVS. Micromeritics, textbook of physical pharmaceutics. 2000; 2(2); 22-24.
24. Banker GS, Rhodes CT. Modern pharmaceutics. 1990; 40: 416-17.
25. Vishnu MP, Bhupendra GP, Patel HV, Patel KM. Mucoadhesive bilayer tablets of propranolol hydrochloride. AAPS Pharm Sci Tech. 2007; 8(3): E203–E208.