

Development and *In Vitro* Evaluation of Buccal Tablet of Quinapril Hydrochloride

Ranade A.N., Ranpise N.S., Sanap G.S and Kulkarni R.R

STES's Sinhgad College of Pharmacy, Vadgaon (Bk.), Pune- 411041, Maharashtra (India).

ABSTRACT

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Quinapril hydrochloride is reported to have low oral bioavailability due to an extensive hepatic first pass effect. In the present work bilayered buccoadhesive tablet of quinapril hydrochloride was prepared. Carbopol® 974P and hydroxypropylmethylcellulose K4M were chosen as the bioadhesive polymers to formulate buccal tablets of the drug. Citric acid was chosen as the permeation enhancer. The formulations were evaluated for weight, hardness, friability, swelling rate, *in vitro* bioadhesion force, *in vitro* residence time, *ex vivo* diffusion study and drug release. The optimized formulation containing 10% Carbopol 974P and 1.2% citric acid was found to give 98.3% drug release at the end of 3 h with a bioadhesion force of 553.9 dynes/cm² and enhancement ratio of 2.6. High flux value in presence of penetration enhancer indicated increased penetration of drug across the buccal mucosa which can result in improved bioavailability.

Keywords: Buccoadhesive tablet, quinapril hydrochloride, permeation enhancer, *ex vivo* diffusion study, *in vitro* bioadhesion force, *in vitro* residence time

INTRODUCTION

Delivery of drugs through various transmucosal routes has gained significant attention owing to their presystemic metabolism or instability in the acidic environment associated with the oral environment. Amongst the various absorptive mucosae, mucosa of the oral cavity is viewed as a convenient and easily accessible site for the delivery of therapeutic agents¹. Rich blood supply, robust nature, short recovery times after stress or damage, lower enzymatic activity of saliva, facile removal of formulation, better patient acceptance and compliance are some other prominent meritorious visages of buccoadhesive systems^{2,3}.

Quinapril hydrochloride is a low dose angiotensin-converting enzyme (ACE) inhibitor used to treat hypertension and heart failure. Quinapril Hydrochloride shows a low bioavailability of 25-30% due to first pass metabolism. It is a drug with log P value of 1.4 and pK_a of 3 which makes it a suitable candidate for oral mucosal drug delivery system⁴. Plasma half life of quinapril hydrochloride is 2 h and it does not have objectionable taste¹. Hence, in this study an attempt is made to develop a double layered quinapril hydrochloride buccal tablet with maximum percent drug release at 3 h, high bioadhesion force (F) and good enhancement ratio (ER). Rational blends of Carbopol® 974P (CP) and hydroxypropylmethylcellulose K4M (HPMC) were chosen

as the polymers to formulate buccal bioadhesive tablet of drug. The polymers selected are well documented to provide regulated drug release and bioadhesion^{5,6,7}.

MATERIALS

Quinapril hydrochloride was provided as gift sample by Aurbindo Pvt. Ltd. (Hyderabad, India), Carbopol® 974P by Lubrizol Ltd. (Mumbai, India) and HPMC by Colorcon Asia Private Limited (Goa, India). Sodium saccharin, ethyl cellulose, citric acid and lactose used were procured by Loba Chemicals Ltd. (Mumbai, India). All other chemicals used in the study were of analytical grade.

METHODS

DSC Studies:

Pure Quinapril Hydrochloride, Carbopol: HPMC(1:1) and Quinapril Hydrochloride : Carbopol : HPMC (1:1:1) were subjected to Differential Scanning Calorimetry Studies to confirm the compatibility between drug and excipients. Studies were carried out using Mettler Toledo DSC in the temperature range of 30-300°C with heating rate of 30°C/min.

Preparation of buccoadhesive tablet of quinapril hydrochloride:

The composition of different buccoadhesive formulations prepared using varying amounts of CP, HPMC, Avicel PH 102 (Microcrystalline cellulose), ethyl cellulose, citric acid, sodium saccharin and lactose are listed in Table No.1. Drug and the excipients were homogeneously mixed and 150 mg of the powder blend was pre-compressed on tablet punching

*Address for Correspondence:

A. N. Ranade, Department of Pharmaceutics, STES's Sinhgad College of Pharmacy, Pune-411041, Maharashtra (India).

Email- aratiranade@rediffmail.com

machine (GMC 6, Mumbai, India) at a pressure of 0.5 ton to form a single layered flat beveled tablets of 8 mm diameter. Further, 10 mg of ethyl cellulose powder was added and final compression was done at a pressure of 3.5 tons to obtain a bilayer tablet.

Evaluation of tablets

Tablet assay:

Twenty tablets were powdered from each batch and a quantity equivalent to 10 mg of quinapril hydrochloride was accurately weighed and extracted with suitable volume of methanol. Each extract was diluted with distilled water and analyzed spectrophotometrically (JASCO, V-530, Japan) at 220 nm. The excipients i.e. HPMC, CP, citric acid, sodium saccharin and lactose were also analyzed, using the highest concentration employed in the formulation, to check their interference at 220 nm.

Physical evaluation:

Twenty tablets from each batch were evaluated for uniformity in tablet weight and thickness. Twenty tablets from each batch were examined for friability using a Roche type friabilator (Electrolab Pvt. Ltd., India) and hardness using a Monsanto type hardness tester (Lab-Hosp, India).

In vitro bioadhesion force study:

The *in vitro* bioadhesion study was carried out using a modification of bioadhesion test assembly described by Gupta *et. al.*⁸. Bioadhesion test apparatus employed for the purpose was a modification of the modified double beam physical balance. Porcine buccal mucosa was used as the model membrane for the measurement of bioadhesive strength. It was fixed to the glass vial using a thread. The vial was lowered into the jacketed glass container filled with buffer pH 6.8 and maintained at $37 \pm 1^\circ\text{C}$. Before carrying out the investigation, the jacketed glass container containing beaker was kept below the right hand setup of the assembly. The tablet was stuck to the lower side of the beaker using acrylate adhesive. The assembly was kept undisturbed for 1 min and the weights were slowly added to the left hand side till the tablet just detached from the membrane surface. The bioadhesion force was calculated in terms of force (dyne/cm^2) required to detach the tablet from the membrane.

In vitro dissolution studies:

In vitro dissolution studies were conducted for all the formulation combinations using USP XXII dissolution testing apparatus paddle method (Type II). Each tablet was inserted in a metal die with a central hole of 8 mm in diameter which was sealed at the lower end with paraffin wax for obtaining unidirectional release⁹. The dissolution test was

performed using 900 ml of phosphate buffer pH 6.8, at $37 \pm 0.5^\circ\text{C}$ and 50 rpm. Aliquots of samples were periodically withdrawn and the sample volume replaced with an equal volume of fresh dissolution medium. The samples were analyzed spectrophotometrically at 220 nm using UV-Visible spectrophotometer (JASCO, V-530, Japan).

Ex vivo diffusion studies:

Ex vivo diffusion study of quinapril hydrochloride tablet was carried out on porcine buccal mucosa using modified Franz diffusion cell. Phosphate buffer pH 6.8 was used as receptor solution. The assembly was stirred magnetically and maintained at $37 \pm 5^\circ\text{C}$. The diffusion was carried out for 3 h. Five ml sample was withdrawn at fixed intervals of 5, 10, 20, 30, 45, 60, 120, 180 min and replaced with an equal volume of phosphate buffer pH 6.8. These aliquots after centrifugation were diluted appropriately and analyzed spectrophotometrically at 220 nm. The graphs of percent cumulative release versus time were plotted. The slope was calculated from the graph. The permeability coefficient and flux values were calculated using following formula¹⁰,

$$\text{Permeability coefficient (P)} = \frac{\text{Slope} \times \text{Volume of donor compartment (V}_d\text{)}}{\text{Surface area of tissue used (S)}}$$

$$\text{Flux (J)} = \text{Permeability coefficient (P)} \times \text{Concentration of donor compartment (C}_d\text{)}$$

$$\text{Enhancement ratio (ER)} = \frac{\text{Permeability coefficient (P) of drug with enhancers}}{\text{Permeability coefficient (P) of drug alone}}$$

In vitro Residence Time:

The mucoadhesive properties of the tablets were evaluated by *in vitro* residence time study as reported by Patel *et al.*¹¹. A 1 cm by 1 cm piece of porcine buccal mucosa was tied onto a glass slide using thread. Tablet was stuck onto the wet, rinsed, tissue specimen, by applying light force with a fingertip for 30 seconds. The prepared slide was hung onto one of the grooves of a USP tablet disintegrating test apparatus. The disintegrating test apparatus was operated such that the tissue specimen was given regular up and down movements in a beaker containing the dissolution medium (pH 6.8 buffer solution). Time required for complete detachment or erosion of tablet from the glass slide was noted.

Swelling Index:

Tablets were weighed individually (designated as w_1) and placed separately in petridishes containing phosphate buffer pH 6.8. 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)¹². The swelling index of each system was calculated using the following formula:

$$\text{Swelling Index} = \frac{W_2 - W_1}{W_1} \times 100$$

Stability Studies:

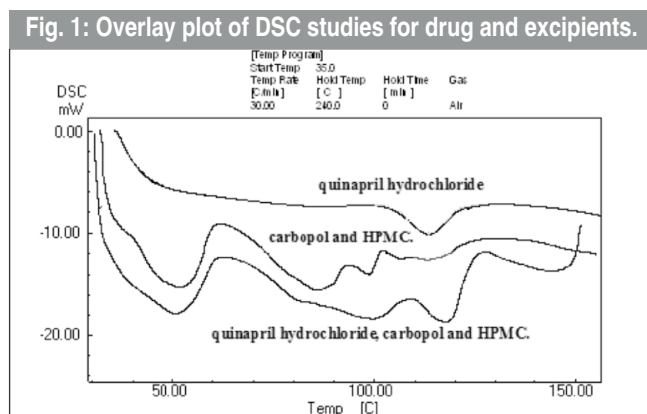
Formulations F7 and F8 were subjected to stability studies. The tablets were packed in PVC (clear)-aluminum blister pack of 10 tablets. These tablets were subjected to stability studies for a period of three months as per ICH guidelines at the ambient temperature and relative humidity (RH) and 40°C and 75% RH conditions. The samples were withdrawn at 0, 7, 15 days, 1, 2 and 3 months for all temperature conditions and evaluated for appearance, *in vitro* residence time studies, *in vitro* bioadhesion force studies, *in vitro* drug release studies and *ex vivo* diffusion studies.

RESULTS AND DISCUSSION

The present study was aimed to achieve the unidirectional release with maximum permeation across buccal mucosa from a double layered buccoadhesive tablet of Quinapril Hydrochloride. This route bypasses the first pass hepatic metabolism, increasing the chances of improved bioavailability. The polymers used in the formulation are well established for buccal route. Polymer selection was done after testing drug excipient compatibility.

Differential Scanning Calorimetry studies:

DSC studies were performed for testing the compatibility between the drug and shortlisted excipients. This study indicated endothermic peak at 122°C for pure quinapril hydrochloride. This peak appears in thermograms of all samples containing quinapril hydrochloride. The thermograms of polymers do not show any sharp or broad peaks in the temperature range of 30°C-300°C (Figure 1) that can be specifically identified. So it can be concluded that the excipients and drug do not interact with each other. Also quinapril hydrochloride doesn't form a complex with the excipients, as the endothermic peaks do not change position



or broaden. Thus compatibility studies proved that drug is compatible with commonly used excipients and based on this result CP was selected as a bioadhesive polymer. HPMC K4M was included in the formulation to obtain tablet integrity. Due consideration was given to release retarding property of HPMC.

After the tablet preparation each tablet was evaluated for various physical characteristics. The shape of tablets of all formulations was circular. Further, tablet weights varied between 160 ± 2.70 mg, thickness between 2.0 ± 0.06 and hardness between 4 and 5 kg/cm². The friability ranged between 0.8 and 0.92 % which is within the set limits of USP. The assay content of quinapril hydrochloride varied between 99.1 and 101.6 %. Thus, all the physical parameters of the tablet were practically within control (Table No.2).

In Vitro Bioadhesion Force:

In vitro bioadhesion force study was carried out with the aim of finding the force required to remove the dosage form from the site of application. The bioadhesion force ranged between 422.6 ± 1.50 dyne/cm² for formulation F1 to 562.4 ± 2.03 dyne/cm² for formulation F9 as shown in Table No.2. These formulations vary in the amount of polymer and permeation enhancer used. The bioadhesion force increased with the increasing amount of polymer CP and permeation enhancer citric acid. Formulation F9 showed maximum *in vitro* bioadhesion force of 562.4 dynes/cm².

In-Vitro Dissolution Studies:

The graph of amount of drug released is shown in Figure 2. The percent drug release at 3 h ranged between 87.6 and 100.1 %. The formulations F7, F8 and F9 showed maximum release of 97.1, 98.3 and 99.1 % drug release respectively (Table No.3). The different kinetic models that were applied to interpret the drug release rate from the tablet are shown in Table No.3. The results of the formulation F2 showed

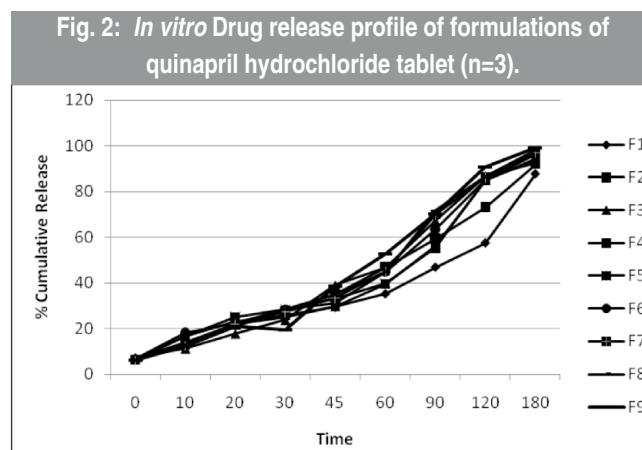
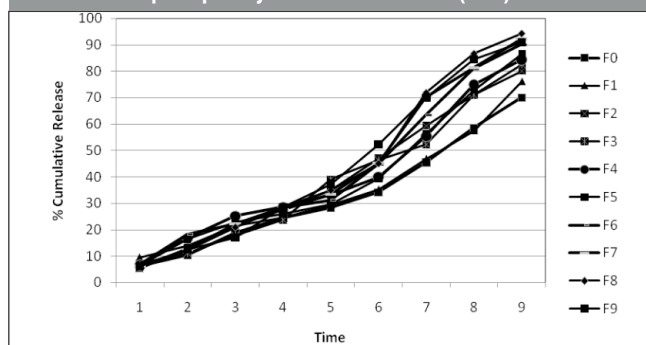


Fig.3: Ex vivo Diffusion profile of formulations of quinapril hydrochloride tablet (n=3).



Korsmeyer Peppas model while remaining formulations from F1 and F3 to F9 showed the Higuchi model. Hence the best fit model for the formulation of quinapril hydrochloride tablet was Higuchi model. According to Higuchi model, the drug release from insoluble matrix is directly proportional to square root of time and is based on fickian diffusion. It reveals that the mechanism of drug release is predominantly diffusion. Smaller correlation coefficient was observed for zero order kinetics and first order kinetics. The overall rate of drug release at 3 h tended to rise with increasing amount of polymer and permeation enhancer.

Ex vivo Diffusion Studies:

Ex vivo diffusion studies were carried out to access the permeation of drug across buccal mucosa. Freshly isolated porcine buccal mucosa was used for this purpose. Diffusion studies were carried out on all the formulations F1 to F9 containing varying amounts of penetration enhancer and compared with diffusion of pure drug. Enhancement ratio was calculated to understand the effect of penetration enhancer. The amount of drug permeated across the porcine buccal mucosa varied between 92.1 and 94.3 % (Fig.3 and Table No.4). The permeability coefficient calculated using the

formula ranged between 0.35 and 0.90 (mg/cm.min) and the flux values ranged between 2.7×10^{-3} and 3.5×10^{-3} (mg/cm².min). The enhancement ratio ranged between 1.57 and 2.32 as shown in Table No.4. The parameters were observed to have inclining trend with the rising amount of polymer and permeation enhancer. The high values of P, J and ER confirm the reliability of diffusion from the formulations. Formulation F8 showed maximum enhancement ratio of 2.6, followed by F7 with a ratio of 2.32. Formulation F9 containing highest percentage of bioadhesive polymer and highest percentage of citric acid showed enhancement ratio of 2.02. This could be because of high solubility of drug due to high percentage of citric acid leading to saturation of drug in donor compartment. Another reason for decreased enhancement ratio could be small surface area of membrane for higher concentration of drug.

In Vitro Residence Time:

In vitro residence time test was performed to calculate the time for which tablet remained adhered to buccal mucosa and also to study the effect of mouth movements on the displacement of dosage form. The *in vitro* residence time calculated ranged between 130 ± 2.5 and 195 ± 1.5 min. The residence time increased with the increasing amount of bioadhesive polymer i.e. CP as given in Table No.2. Formulations F7, F8 and F9 showed *in vitro* residence time of more than 180 minutes. This confirms that formulation will be retained at the site of application for the entire duration for which drug release is proposed.

Swelling Index:

Swelling index test gave idea of swelling behavior of the tablet which can be related to extent of drug release. Swelling index calculated from the formula ranged between 70 and 90%. The swelling index of the tablet enhanced slowly with the increasing amount of CP as reported in Table No.2. Based

Table 1: Composition of quinapril hydrochloride tablets.

| Formulation Ingredients | Formulations and Quantity (mg) | | | | | | | | |
|----------------------------|--------------------------------|------|------|-------|-------|-------|-------|------|------|
| | F1 | F2 | F3 | F4 | F5 | F6 | F7 | F8 | F9 |
| Quinapril hydrochloride | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 |
| Carbopol 974P | 7.5 | 7.5 | 7.5 | 11.25 | 11.25 | 11.25 | 15 | 15 | 15 |
| HPMC K4M | 10.5 | 10.5 | 10.5 | 10.5 | 10.5 | 10.5 | 10.5 | 10.5 | 10.5 |
| Avicel PH 102 | 30 | 30 | 30 | 30 | 30 | 30 | 30 | 30 | 30 |
| Saccharin sodium | 1.5 | 1.5 | 1.5 | 1.5 | 1.5 | 1.5 | 1.5 | 1.5 | 1.5 |
| Citric acid | 0.45 | 1.8 | 3 | 0.45 | 1.8 | 3 | 0.45 | 1.8 | 3 |
| Lactose | 90.05 | 88.7 | 87.5 | 86.3 | 84.95 | 83.75 | 82.55 | 81.2 | 80 |
| Ethyl cellulose | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 |
| Total | 160 | 160 | 160 | 160 | 160 | 160 | 160 | 160 | 160 |

Table 2: Evaluation parameters of quinapril hydrochloride tablets.

| Evaluation parameters | Formulations | | | | | | | | |
|---|--------------|------------|------------|------------|------------|------------|------------|------------|------------|
| | F1 | F2 | F3 | F4 | F5 | F6 | F7 | F8 | F9 |
| Tablet Diameter (mm) | 8 | 8 | 8 | 8 | 8 | 8 | 8 | 8 | 8 |
| Tablet Hardness (Kg/cm ²) | 4-5 | 4-5 | 4-5 | 4-5 | 4-5 | 4-5 | 4-5 | 4-5 | 4-5 |
| Tablet Thickness (mm) | 2 ± 0.03 | 2 ± 0.04 | 2 ± 0.05 | 2 ± 0.03 | 2 ± 0.02 | 2 ± 0.04 | 2 ± 0.03 | 2 ± 0.02 | 2 ± 0.03 |
| Friability (%) | 0.8 | 0.82 | 0.8 | 0.84 | 0.9 | 0.86 | 0.81 | 0.88 | 0.92 |
| Swelling Index (%) | 70 | 70 | 75 | 70 | 80 | 70 | 80 | 90 | 90 |
| <i>In Vitro</i> Bioadhesion Force Study (dyne/cm ²) | 422.6±1.50 | 451.3±1.61 | 459.2±1.76 | 468.4±1.89 | 474.6±1.25 | 508.8±1.95 | 545.4±1.20 | 553.9±1.66 | 562.4±2.03 |
| <i>In Vitro</i> Residence Time Study (min) | 130 ± 2.5 | 140 ± 1.9 | 150 ± 2.5 | 160 ± 1.5 | 165 ± 2.0 | 170 ± 2.5 | 180 ± 1.5 | 190 ± 1.6 | 195 ± 1.5 |

Table 3: Percent drug release (n=3± SD) of various formulations with best fit model

| Time | F1 | F2 | F3 | F4 | F5 | F6 | F7 | F8 | F9 |
|-----------------------|-------------|-------------------|-------------|-------------|-------------|-------------|-------------|-------------|-------------|
| 0 | 6.6 ± 0.10 | 6.4 ± 0.80 | 7.3 ± 0.22 | 6.4 ± 0.54 | 6.4 ± 0.44 | 6.7 ± 0.32 | 6.2 ± 0.11 | 6.5 ± 0.58 | 6.1 ± 0.19 |
| 10 | 14 ± 0.23 | 13.2 ± 0.12 | 11.3 ± 0.45 | 16.7 ± 0.43 | 16.6 ± 0.15 | 18.2 ± 0.55 | 12.5 ± 0.23 | 12.4 ± 0.59 | 12.6 ± 0.28 |
| 20 | 21.7 ± 0.34 | 21.6 ± 0.45 | 17.8 ± 0.29 | 25.1 ± 0.33 | 23 ± 0.41 | 22.2 ± 0.36 | 22.2 ± 0.34 | 21 ± 0.38 | 21 ± 0.37 |
| 30 | 24.8 ± 0.34 | 27.7 ± 0.36 | 23.7 ± 0.17 | 28.5 ± 0.78 | 25.9 ± 0.67 | 28.3 ± 0.78 | 27.3 ± 0.87 | 28.5 ± 0.90 | 19.4 ± 0.45 |
| 45 | 29.4 ± 0.65 | 34.9 ± 0.22 | 39 ± 0.44 | 33.1 ± 0.62 | 29.7 ± 0.33 | 31.1 ± 0.55 | 33.4 ± 0.49 | 35 ± 0.51 | 38.3 ± 0.52 |
| 60 | 35.3 ± 0.55 | 47 ± 0.41 | 46.5 ± 0.11 | 39.9 ± 0.45 | 39.4 ± 0.13 | 44.7 ± 0.49 | 45.1 ± 0.77 | 45.1 ± 0.24 | 52.4 ± 0.99 |
| 90 | 46.9 ± 0.26 | 59.4 ± 0.67 | 67.3 ± 0.88 | 55.3 ± 0.91 | 56.2 ± 0.55 | 63.3 ± 0.65 | 69.9 ± 0.91 | 71.9 ± 0.66 | 70 ± 0.65 |
| 120 | 57.5 ± 0.66 | 73.1 ± 0.78 | 86.9 ± 0.61 | 84.9 ± 0.65 | 84.9 ± 0.56 | 84.9 ± 0.43 | 86.3 ± 0.55 | 86.7 ± 0.45 | 90.6 ± 0.76 |
| 180 | 87.6 ± 0.45 | 91.8 ± 0.57 | 92.5 ± 0.57 | 93.4 ± 0.56 | 94.5 ± 0.31 | 96.1 ± 0.39 | 97.1 ± 0.67 | 98.3 ± 0.54 | 99 ± 0.87 |
| Kinetic model Higuchi | Higu chi | Korsm eyer Peppas | Higuchi | Higuchi | Higuchi | Higuchi | Higuchi | Higuchi | Higuchi |

on the results of all the parameters, formulations F7 and F8 were scaled up for the purpose of stability studies.

Stability Studies:

Tablets from formulations F7 and F8 batches were subjected to accelerated temperature and humidity conditions as per ICH guidelines. Stability studies were carried out for the period of three months. For formulation F7, the tablets released the drug over a period of 3 h at the end of 90 days when kept at room temperature. The total drug release was 92.2% which was similar to the initial total drug release of 92.3%. The permeability coefficient, flux and enhancement ratio was 0.80 mg/cm.min, 4.0×10^{-3} mg/cm².min and 2.34 respectively which was similar to the initial values. Also, at 40°C and 75% RH the tablets showed total drug release of 92.2% which was similar to the initial total drug release. The permeability coefficient, flux and enhancement ratio was 0.82 mg/cm.min, 4.14×10^{-3} mg/cm.min and 2.32 respectively which were similar to the initial values. For formulation F8, the tablets released the drug over a period of 3 h at the end of 90 days when kept at room temperature. The total drug release was 94.5%, which was similar to the initial total drug release of 94.3%. The permeability coefficient, flux and enhancement ratio was 0.91 mg/cm.min, 4.54×10^{-3} mg/cm².min and 2.62 respectively which was similar to the initial values. Also, the tablets released the drug over a period of 3 h at the end of 90 days when kept at 40°C and 75% RH, the total drug release was 94.4%, which was similar to the initial total drug release of 94.3%. The permeability coefficient, flux and enhancement ratio was 0.91 mg/cm.min, 4.53×10^{-3} mg/cm².min and 2.63 respectively which was similar to the initial values. At the end of three months, both the formulations were found to be stable for all other parameters. Also no physical changes in the tablet were seen after 3 months of storage under room temperature and 40°C and 75% RH. Based on the results of evaluation parameters during stability studies it can be concluded that formulation F8 is more stable than F7 formulation having high enhancement ratio. Also this stability study indicates that quinapril hydrochloride is stable in presence of the excipients used at high temperature and in presence of high humidity.

CONCLUSION

The study suggests that the buccoadhesive tablet of quinapril hydrochloride prepared using CP and HPMC provided regulated release upto 3 h. The tablet demonstrated ample bioadhesive strength with porcine buccal mucosa. Formulations F7 was found to be the best formulations to achieve the aim of this study. Stability studies for a period of 3 months demonstrated no considerable difference in performance characteristics. High flux value in presence of

penetration enhancer indicated increased penetration of drug across the buccal mucosa which can result in improved bioavailability.

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REFERENCES

1. Bandyopadhyay AK. Advances in Buccal Adhesive Drug Delivery. *Drug Delivery Technology*. 2006;6(6):51-5.
2. Shojaei AH. Buccal Mucosa as a route for systemic drug delivery: A Review. *J. Pharm. Pharmaceut. Sci.* 1998;1(1):15-30.
3. Khanna R, Agarwal SP, Ahuja A. Mucoadhesive buccal drug delivery: A Potential alternative to conventional therapy. *Ind. J. Pharm. Sci.* 1998;60(1):1-11.
4. Rossi S, Sandri G. Buccal drug delivery: A challenge already won?. *Drug delivery/Formulation and technology*. 2005:59
5. Kadam P, Dias R, Mali K. Formulation and evaluation of buccoadhesive tablets of atenolol. *J. Pharm. R.* 2008;1(2):193-9.
6. Munasur AP, Pillay V, Chetty DJ. Statistical optimization of the mucoadhesivity and characterization of multipolymeric propranolol matrices for buccal therapy. *Int. J. Pharm.* 2006;323:43-51.
7. Swarbrick J, Boylan JC. *Encyclopedia of Pharmaceutical Technology*. New York: Marcel Dekker, 1990:189-208.
8. Gupta A, Garg S, Khar RK. Measurement of bioadhesive strength of mucoadhesive buccal tablets: Design of an in-vitro assembly. *Indian Drugs* 1992;30:152-5.
9. Yilmaz Capan *et al*. Design and Evaluation of sustained release and buccal adhesive propranolol hydrochloride tablets. *J. Cntrl. Rel.* 1996;38: 11-20
10. Lalla J, Gurnaney R. Permeation of diclofenac through buccal mucosa. *Ind. J. Pharm. Sci.* 2002;64(4):373-7.
11. Patel VM, Prajapati BG, Patel KM. Mucoadhesive bilayer tablets of propranolol hydrochloride. *AAPS Pharm. Sci. Tech.* 2007;8: Article 77.
12. Desai K, Kumar T. Preparation and evaluation of novel buccal adhesive system. *AAPS Pharm. Sci. Tech.* 2004;5(3):Article 35.
