

DESIGN AND DEVELOPMENT OF MUCOADHESIVE BUCCAL DELIVERY FOR PANTOPRAZOLE WITH STABILITY ENHANCEMENT IN HUMAN SALIVA

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Received: 27 Jan 2013, Revised and Accepted: 06 Mar 2013

ABSTRACT

Objective: Pantoprazole undergoes hepatic first pass metabolism, hence it shows poor bioavailability. Stability of Pantoprazole in human saliva was improved using magnesium oxide due to its strong waterproofing effect. In present study attempt has been done to improve the bioavailability by formulating mucoadhesive buccal tablet as well as to improve stability of tablet in human saliva.

Methods: Nine formulations were developed with varying concentrations of polymers like Sodium alginate and HPMC. To determine the effect of selected excipients on the release of pantoprazole a full factorial design 3² was setup.

Results: The formulations were evaluated for weight variation, hardness, surface pH, drug content uniformity, swelling index, and bioadhesive strength and *in-vitro* drug dissolution study. FTIR studies showed no evidence of interactions between drug and excipients. The maximum *in-vitro* drug release profile was achieved with the formulation F6 which contains the drug, Sodium alginate and HPMC K4M in the (20/17/8) mg respectively. The surface pH, bioadhesive strength and drug content of formulation F6 was found to be 7.1, 27.9, and 98.0 % respectively. The formulation F6 exhibited sustained drug release i.e. 98.009 % in 6 h and 80.12 % drug diffusion in 8 h through the sheep buccal mucosa. The *in vitro* release kinetics studies reveal that formulations fit well with zero order kinetics and mechanism of drug release is non-Fickian diffusion.

Conclusion: It is concluded that magnesium oxide stabilize the pantoprazole buccal tablet in human saliva for at least 6 h and also improves oral bioavailability.

Keywords: Pantoprazole, Mucoadhesive buccal tablet, Sodium alginate, Bioadhesive strength, *In vitro* drug release, Release Kinetics.

INTRODUCTION

Buccal drug delivery is an alternative route for the oral administration of drugs which undergo degradation in the gastrointestinal track or hepatic first pass metabolism. Buccal drug delivery offers a safer mode of drug delivery system and the dosage form can be removed in case of toxicity. Buccal mucosa has an excellent accessibility, which leads to direct access to systemic circulation through the internal jugular vein which bypasses the drugs from hepatic first pass metabolism. [1]

Pantoprazole sodium sesquihydrate (PSS) it is chemically known as sodium 5- (difluoromethoxy) - 2 - [[[(3, 4-dimethoxy-2-pyridinyl) methyl] sulfinyl]-1H-benzimidazole sesquihydrate.[2] It exhibits potent and long-lasting inhibition of gastric acid secretion by selectively interacting with the gastric proton pump (K⁺/H⁺-ATPase) in the parietal cell secretory membrane.[1-3] It is used for treatment of erosion and ulceration of the esophagus caused by gastro esophageal reflux disease. However, the bioavailability of Pantoprazole following oral administration is usually very low, since it degrades very rapidly in the acidic environment of stomach and undergoes hepatic first pass metabolism. To improve the bioavailability of Pantoprazole, in particular by preventing gastric degradation, various oral formulations of Pantoprazole such as enteric coated granule and tablet have been developed with a subsequent 40% increase in oral bioavailability of pantoprazole in humans.[4-5] However, these oral formulations of pantoprazole have been known to have a wide individual variation of plasma concentration in human subjects. Thus, attempts were made to develop alternative dosage forms such as rectal suppository and buccal adhesive tablet, since the gastric degradation and first-pass metabolism of Pantoprazole may be avoided via these routes of administration. In particular, Pantoprazole buccal adhesive tablets were developed to be attached to the human cheek without collapse and with stability enhancement in human saliva for at least 6 h. [4-9]

The buccal adhesive tablets were prepared by mixing sodium alginate, hydroxyl propyl methylcellulose (HPMC) and magnesium oxide. Stability of Pantoprazole tablet in human saliva could not be achieved by using conventional buccal adhesive ingredients.[3,4]

The enhanced stability of Pantoprazole tablet in human saliva was attributed to magnesium oxide. The bioadhesive force was controlled by altering the composition ratio of sodium alginate to HPMC. However, previous studies were focused on controlling the physicochemical properties such as the bioadhesive forces of Pantoprazole buccal adhesive tablets and the stability of Pantoprazole in human saliva. There has been a lack of information on the release of pantoprazole from the tablets and the absorption of drug from the oral cavity. Furthermore, we investigated the release of Pantoprazole from buccal adhesive tablets and the absorption of Pantoprazole delivered by the buccal adhesive tablets composed of the sodium alginate, HPMC, magnesium oxide, soluble starch. [2-4]

MATERIALS AND METHODS

Materials

Pantoprazole sodium sesquihydrate (PSS) was a gift sample from Liben Pharmaceutical Pvt. Ltd., Akola. Sodium alginate, HPMCK4M, Magnesium Oxide & Soluble starch was purchased from Loba chemicals, Mumbai. All other reagents used were of analytical grade.

Methods

Preformulation study

Calibration of Pantoprazole [2-10]

A stock solution of pantoprazole is prepared by dissolving 10 mg drug in 100 ml of 0.1 N HCl & PH 6.8 phosphate buffer. From this stock solution, suitable dilutions were prepared using the same solvent in the range if 5-30 µg/ml. The λ max of the drug was determined by scanning one of the dilutions between 400 and 200 nm using a UV-visible spectrophotometer (simadzu-1800). The absorbance of all the other solutions is measured in 0.1 N HCl and phosphate buffer PH 6.8. Standard curve between concentration and absorbance was plotted and intercept (B) and slope (K) values were noted.

i) **In 0.1 N HCl:** Drug is calibrated in 0.1 N HCl by using UV-Spectrophotometer with different dilutions at determined wavelength.

- ii) **In PH 6.8 Phosphate buffer:** Drug is calibrated in PH 6.8 Phosphate buffer by using UV-Spectrophotometer with different dilutions at determined wavelength.

Preparation of mucoadhesive buccal tablets

Mucoadhesive buccal tablets, each containing 20 mg Pantoprazole sodium sesquihydrate (PSS) were prepared by direct compression method. Composition of various formulations employing Sodium alginate, HPMC K4M, Magnesium oxide & Soluble Starch are very important in the formulation. To determine the effect of selected excipients on the release of pantoprazole a full factorial design 3² (DX 8.0.5.2 version was used to generate the factorial design) was setup. All the batches were prepared which is shown in Table 1. All

the ingredients of tablets were blended in glass mortar with a pestle for 15 min to obtain uniform mixture. The blended powder was then compressed into 100 mg tablets (at 5-6 kg/cm²) on a single stroke, 10 station rotary tablet machine (Cadmach Machinery Co. Pvt. Ltd., Ahmadabad, India) with 6 mm round shaped flat punch.

Compatibility studies

The drug-excipient compatibility studies were carried out using Fourier Transform Infrared Spectrophotometer (Jusco, FT/IR-4100). IR spectra of pure drug and excipients were recorded. A base line correction was made using dried potassium bromide and then the spectra of the dried mixture of drug, formulation mixture were recorded by using FTIR. [10-12]

Table 1 : List of Ingredients in Formulations

Ingredients (mg) /Formulation	F1	F2	F3	F4	F5	F6	F7	F8	F9
Pantoprazole sodium sesquihydrate	20	20	20	20	20	20	20	20	20
Sodium alginate	15	15	15	17	17	17	19	19	19
HPMC K4M	4	6	8	4	6	8	4	6	8
Magnesium Oxide	50	50	50	50	50	50	50	50	50
Starch	11	9	7	9	7	5	7	5	3
Total	100	100	100	100	100	100	100	100	100

Stability of Pantoprazole tablet in human saliva

The human saliva was prepared by filtering natural human saliva. Pantoprazole tablets were prepared by different alkali materials like magnesium oxide, potassium phosphate monobasic, sodium phosphate monobasic and sodium phosphate dibasic. Each pantoprazole tablet was immersed in 5 ml of filtered human saliva and then taken out at predetermined time intervals. The stability of pantoprazole tablet was then evaluated by the change of color and shape and pantoprazole content. [3-4]

Evaluation of Mucoadhesive Tablets of Pantoprazole [6-25]

Hardness

Tablets were evaluated for their hardness using Monsanto hardness tester. The experiment was performed in triplicate and average value was calculated.

Weight variation

Ten tablets from each formulation were weighed using an electronic digital balance (simadzu) and the average weight was calculated. The experiment was performed in triplicate and average value was calculated.

Thickness

Tablets were evaluated for their thickness using digital Vernier callipers. The experiment was in triplicate and average value was calculated. The experiment was performed in triplicate and average value was calculated. [6]

Friability

The friability test was done using Roche's Friabilator. Ten tablets were selected and weighed individually. Then the friability test was carried out at 25 rpm for 4 min. These tablets were then again weighed and percentage loss in weight was calculated. The experiment was performed in triplicate and average value was calculated.

$$\% \text{ Loss} = \frac{\text{Initial Weight} - \text{Final Weight}}{\text{Initial Weight}} \times 100$$

Content uniformity

The tablet was kept in 100 ml volumetric flask containing phosphate buffer pH 6.8 for 24 h. After the tablet was completely dissolved then solution was centrifuged. The supernatant was taken and the absorbance was measured by using UV at 285.2 nm. Dilution was

done by pH 6.8 phosphate buffer, when required. The experiment was performed in triplicate and average value was calculated.

Surface pH

The surface pH of the formulation was determined in order to investigate their possible side effects *in vivo*. An acidic or alkaline formulation will cause irritation of the mucosal membrane and hence this is an important parameter in developing a mucoadhesive dosage form. A combined glass electrode was used for determination of surface pH. The tablets were first allowed to swell by keeping them in contact with 5 ml phosphate buffer pH 6.8 for two hours in 10 ml beakers. Then pH was noted by bringing the electrode near the surface of the formulation and allowing equilibrating for 1 min. The experiment was performed in triplicate and average value was calculated.

In vitro swelling studies

For conducting the study, a tablet was weighed and placed in a Petri-dish containing 5 ml of phosphate buffer at pH 6.8 for 6 h, the tablets were taken out from the Petri-dish and excess water was removed carefully by using filter paper. The swelling Index was calculated using the following formula. The experiment was performed in triplicate and average value was calculated

$$\text{Swelling Index (SI)} = \frac{(W_t - W_o)}{W_o} \times 100$$

Where SI = Swelling index.

W_t = Weight of tablets after time at 't'.

W_o = Weight of tablet before placing in the beaker.

In vitro mucoadhesive study

Mucoadhesive strength of the tablets was measured on a modified two-arm physical balance. The Sheep buccal mucosa was used as biological membrane for the studies. The Sheep mucosa was obtained from the local slaughter house and stored in pH 6.8 buffer. The membrane was washed with distilled water and then with phosphate buffer pH 6.8 at 37°. The Sheep buccal mucosa was cut into pieces and washed with phosphate buffer pH 6.8. A piece of buccal mucosa was tied to the glass vial, which was filled with phosphate buffer. The glass vial was tightly fitted into a glass beaker (filled with phosphate buffer pH 6.8 at 37 ± 0.5°), so that it just touches the mucosal surface. The buccal tablets were suck to lower side of a rubber stopper. The two side of the balance were made equal before the study, by keeping a 5 g, was removed from the right-hand pan, which lowered the pan along with the tablet over the mucosa. The balance was kept in the position for 1 min contact time.

Mucoadhesive strength was assessed in terms of weight (g) required to detach the tablet from the membrane. Mucoadhesive strength which was measured as force of adhesion in Newton's by using following formula was used the experiment was performed in triplicate and average value was calculated.

Force of adhesion (N) = Mucoadhesive strength / 100 X 9.81

In vitro drug release study from the formulated tablet

The *in vitro* drug release studies were performed using Electro lab dissolution test apparatus USP (TDT-08L) paddle type. Dissolution study was carried out for 6 h, at $37 \pm 0.5^\circ$, 100 rpm, in Phosphate buffer pH 6.8, volume of the dissolution media 900 ml. Samples 5 ml each were withdrawn after every 1 h for 6 h. The sink condition was maintained by 5 ml of fresh buffer. The samples were collected in test tubes after filtration through wattman filter paper. The amount of the drug in the aliquots was quantified by taking the absorbance of the sample at 285.2 nm spectrophotometrically, using phosphate buffer pH 6.8 as the blank.[5]

Ex vivo Permeation Study [18]

In this study, sheep buccal mucosa was used as a membrane. Diffusion studies were carried out by using glass surface Franz diffusion cell of capacity 7 ml. Sheep buccal mucosa was obtained from local slaughter house, the tissue was stored in phosphate

buffer pH 6.8 solutions. The epithelium was separated from underlying connective tissues with surgical scissors clamped between donor and receiver chamber of diffusion cells for permeation studies. The smooth surface of mucosa should face the donor chamber and receiver chamber was filled with phosphate buffer of 6.8 pH. Whole assembly was placed in water circulation maintained at $37 \pm 0.5^\circ$. Buccal epithelium was allowed to stabilization for period of 1hr and hydrodynamic in receiver chamber was maintained by stirring with magnetic bead at 50 rpm. After the stabilization of buccal epithelium, the tablet was kept on buccal epithelium and 7ml of phosphate buffer of pH 6.8 was added in donor chamber. The sample of 1 ml were withdrawn at the time interval of 1 h up to 8 h and replaced with equal volume of fresh dissolution medium. The sink condition was maintained throughout the study. The withdrawn sample was diluted to 5 ml. The amount of pantoprazole was determined by UV Spectrophotometer at 285.5 nm. The experiment was performed in triplicate.[1-12]

RESULT & DISCUSSION

Calibration of PAN

Calibration of Pantoprazole was performed in 0.1 N HCl & pH 6.8 phosphate buffer. The R^2 values 0.9995 and 0.9982 were found respectively, which is linear are shown in Fig.1 (A) & (B) respectively.

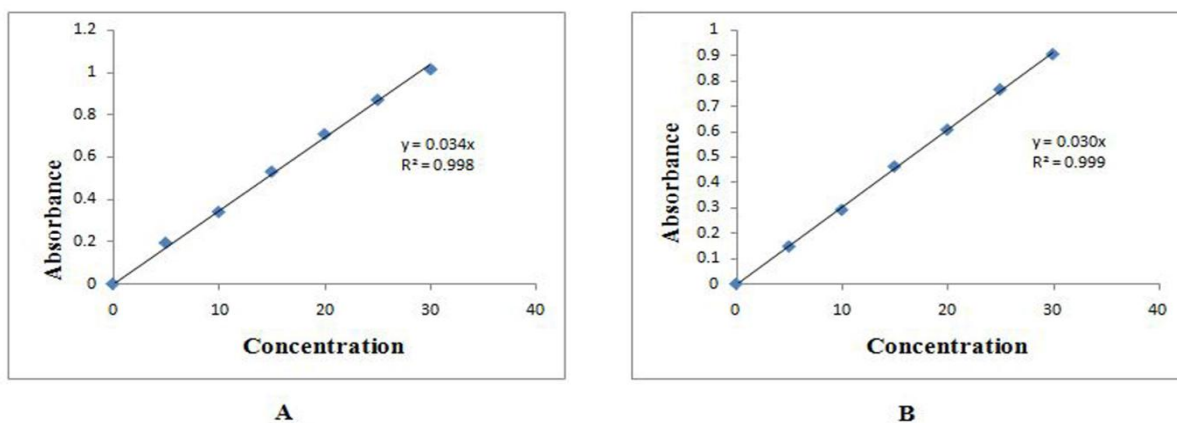


Fig. 1: Calibration Curve's of (A)-Pantoprazole in 0.1 N HCl & (B) - PAN in pH 6.8 Phosphate Buffer

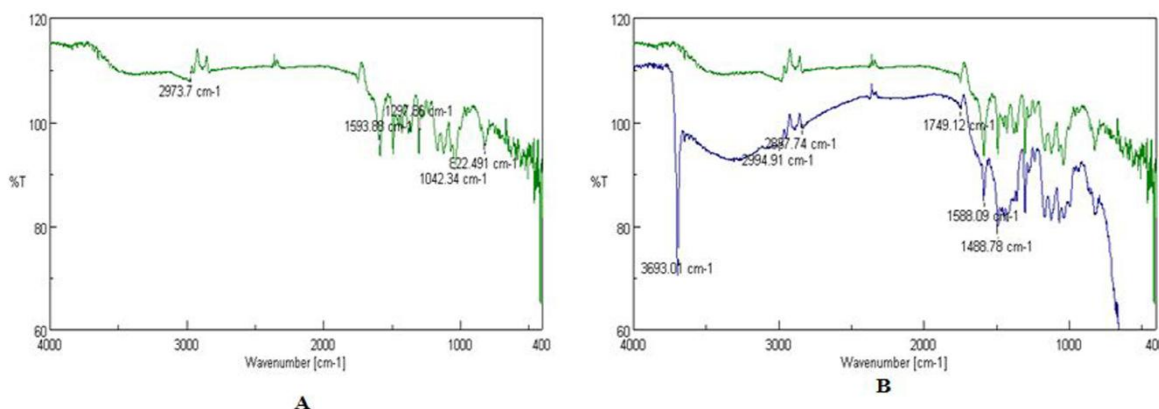


Fig. 2: IR Spectra of (A) -Pantoprazole & (B) - Pantoprazole with combination of Excipients.

Compatibility of Drug and Excipients

Before designing various formulations, the drug polymer-excipient compatibility studies were conducted by FTIR spectroscopy and the results are presented in Fig. 2. The results indicate that there were no chemical incompatibility between drug-polymer, polymer-polymer and polymer-excipients. Total Nine different formulations (F1 to F9) of Pantoprazole buccal tablets were prepared by direct compression techniques using various proportions of polymers and

excipients. In order to select the best formulations, various evaluation parameters were checked.

Stability of Pantoprazole in alkali

To stabilize the pantoprazole tablets in human saliva, pantoprazole tablets were prepared by pressing 20 mg of pantoprazole, 50 mg of sodium alginate and 30 mg of alkali materials such as magnesium oxide, potassium phosphate monobasic, sodium phosphate

monobasic and sodium phosphate dibasic. In the formulation of oral enteric-coated pantoprazole granules and tablets, these alkali materials have been used as stabilizers of pantoprazole. They prevented the decomposition of pantoprazole in acidic gastric fluid which penetrated into the enteric coating walls, since they provided the alkali environment for pantoprazole. In the formulation of the pantoprazole buccal adhesive tablet, these alkali materials were also used as stabilizers of pantoprazole, since pantoprazole is decomposed in weakly acidic or neutral human saliva as well as in acidic gastric fluid. The tablets with potassium phosphate mono basic, sodium phosphate monobasic and sodium phosphate dibasic collapsed at 1 h, with the result that they could not stabilize the pantoprazole buccal adhesive tablets. On the other hand, the tablet with magnesium oxide did not collapse in human saliva until after 6 h. These results suggested that magnesium oxide could be a good stabilizer for pantoprazole buccal adhesive tablets in human saliva. A hydrophobic and insoluble alkali material, magnesium oxide, might protect the human saliva from penetrating into the tablet matrix due to its strong waterproofing effect. To determine the amounts of magnesium oxide that are enough to stabilize the drug in human saliva, the tablets were prepared by compressing 20 mg of pantoprazole and various concentration of magnesium oxide, and their physicochemical properties such as stability in human saliva were evaluated. Magnesium oxide 50 mg gives sufficient stability in human saliva up to 6 h.

Hardness & Thickness

Hardness

The hardness of tablets of different formulation (F1 to F9) was determined as per standard procedure. The average hardness of tablets was found to be 5.0 to 5.66 kg/cm². None of the formulations showed deviation for any of the tablets tested. The result was shown in Table 2.

Thickness of tablets

The average thickness of tablets (F1 to F9) determined and results are presented in Table 2. The maximum and minimum average thickness of tablet was found to 2.19 mm and 2.27 mm. None of the formulation (F1 to F9) deviated from the standards.

Friability

Percentage weight loss in friability test was in the range 0.2% to 0.5% in nine batches prepared by direct compression. The

experiment was performed in triplicate and average value was calculated.

Content uniformity

The content uniformity of the entire tablet (F1 to F9) was evaluated and the results are presented in Table 2. The maximum and minimum percentage of drug content from the different formulations was found to be 99.16, 97.50 % respectively. Hence it is concluded that all the formulations are falling within the pharmacopoeial limits.

Surface pH

The surface pH of tablets of each formulation (F1 to F9) was tested and the results are provided in Table 2. The maximum and minimum pH values of the formulations were found to be 7.1 and 6.9 respectively. The acceptable pH of saliva is in the range of 5-7 and the surface pH of all tablets is within limits. Hence the formulations may not produce any irritation to the buccal mucosa.

In vitro swelling studies

Swelling index of buccoadhesive tablets were performed by agar plate method. Swelling index was calculated with respect to time the swelling index increased as weight gain by tablets increased proportionally with rate of hydration or erosion of polymers in swelling medium. All formulation batches showed 60-65% swelling at 6 hours. The experiment was performed in triplicate and average value was calculated.

In-vitro mucoadhesion studies

The *in-vitro* mucoadhesive strength study was performed by using specially modified physical balance to measure the force (N) required to detach the tablet. The adhesion was mainly affected by the concentration of mucoadhesive polymer. The results were shown in the Table 2. In the formulations F6 sodium alginate concentration increased, the mucoadhesive strength increased. The higher bioadhesive strength of the F6 formulation is observed.

In vitro drug release study from the formulated tablet

The *in vitro* drug release profile of formulation F1- F9 was performed. Among these nine formulations, F6 was found to be highest percentage drug release was shown in Fig.3 (A). During the study it was observed that the tablets were initially swell and no erodible over the period of 6 h.

Table 2: Thickness, Hardness, Drug Content, pH, Mucoadhesive Strength and Weight Variation of Formulation

Code	Avg. Thickness (mm)	Hardness (kg/cm ²)	% Drug Content	Surface pH	Mucoadhesive strength (g)	Weight Variation
F1	2.27 ±0.04	5.33 ±0.02	99.16± 0.009	6.9 ± 0.1	26.9± 0.08	100± 0.8
F2	2.20 ±0.08	5.66 ±0.01	97.50± 0.04	7.0 ± 0.2	27.4± 0.3	101± 0.8
F3	2.20 ±0.08	5.0 ±0.4	98.16± 0.08	7.1 ± 0.08	26.7± 0.4	101± 0.8
F4	2.20 ±0.08	5.33 ±0.02	99.00± 0.2	7.0 ± 0.1	26.4± 0.3	100± 0.4
F5	2.19±0.01	5.5 ±0.7	97.66± 0.01	7.1 ± 0.2	26.9± 0.08	100± 0.2
F6	2.21 ±0.01	5.66 ±0.03	98.00± 0.2	7.1 ± 0.08	28.9± 0.4	101± 0.8
F7	2.19 ±0.00	5.5 ±0.4	98.16± 0.03	6.9 ± 0.08	27.8± 0.1	101± 0.8
F8	2.19 ±0.00	5.5 ±0.5	98.33± 0.02	6.9 ± 0.2	26.4± 0.4	100± 0.8
F9	2.21 ±0.04	5.33 ±0.04	98.50± 0.4	7.0 ± 0.2	27.1± 0.4	101± 0.8

Table 3: Release Kinetics of Formulations

Formulations	Zero Order R ²	First Order R ²	Matrix R ²	Peppas R ²	Hix. Crow R ²	Hix. Crow 'n' values	Best fit Model
F1	0.9956	0.9791	0.9332	0.9933	0.9916	1.068	Zero
F2	0.9934	0.9846	0.9457	0.9861	0.9955	1.024	Hix. Crow
F3	0.9966	0.9746	0.9412	0.9957	0.9912	0.9912	Zero
F4	0.9949	0.9682	0.9343	0.9823	0.9847	0.9372	Zero
F5	0.9780	0.9866	0.9399	0.9923	0.9898	1.0358	Peppas
F6	0.9980	0.8784	0.9299	0.9965	0.9479	0.9452	Zero
F7	0.9870	0.9838	0.9404	0.9935	0.9931	0.9632	Peppas
F8	0.9696	0.9830	0.9591	0.9933	0.9948	0.9131	Hix. Crow
F9	0.9952	0.8505	0.9118	0.9947	0.9189	0.9952	Zero

Drug release kinetics

In-vitro drug release data of F1 to F9 were fitted to zero order, first order, Hix. Crow and Korsmeyer-Peppas equations to ascertain the pattern of drug release. The results shown in Table 3. The R^2 values were found to be higher in zero-order followed by Korsmeyer-

Peppas, Hix. Crow., which indicates the Formulation F6 zero-order release pattern. The results were shown in Fig.3 (B). Also maximum drug release 98.009 % According to Korsmeyer-Peppas equation, the release exponent "n" value is < 0.5 , which indicates the mechanism of drug release for all formulations is non-Fickian diffusion type (PCP Disso V 2.08).

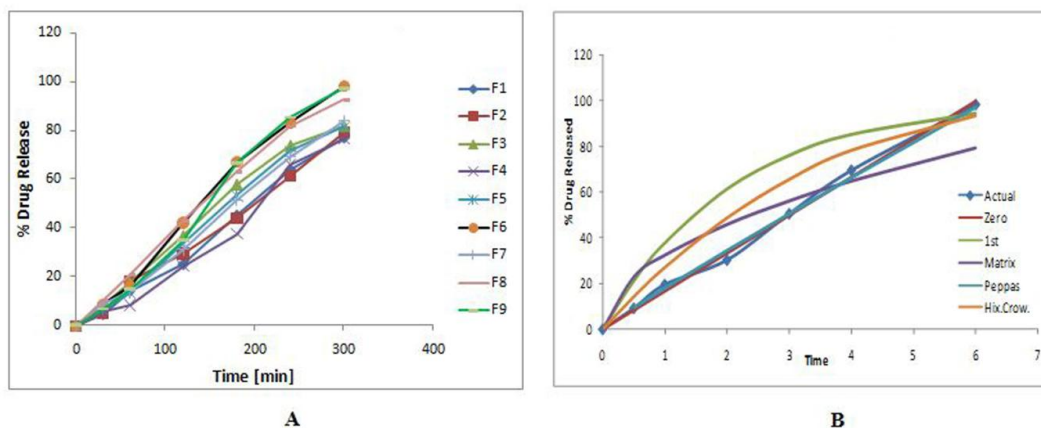


Fig. 3: (A) Drug Release Profile of Formulation (F1-F9) & (B) Release Kinetics of Formulation F6

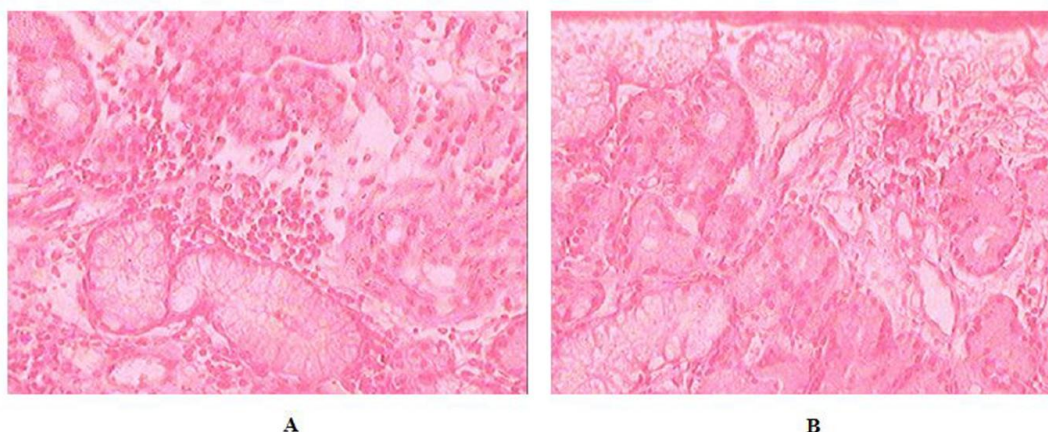


Fig. 4: Histopathology of Sheep Buccal mucosa (A) - Before Permeation & (B) - After Permeation study

Ex vivo Permeation

The *Ex-vivo* buccal permeation study of optimized batch F6 was carried out, to evaluate permeability of Pantoprazole across the buccal mucosal membrane. The permeability data for Pantoprazole are shown in Table 4 indicating that the buccal tablet (F6) diffused maximum 80.12 % drug in 8 h through the membrane. The combination of sodium alginate and HPMC K4M having good bioadhesion thus it adheres and creates the strong bonding with mucus layer and on hydration of the tablet with phosphate buffer 6.8, drug get diffused into the acceptor compartment.

Table 4: Data for % Drug Permeability of Pantoprazole (Batch F6)

Time (h)	% Drug permeability
0	0
1	15.64±0.5
2	18.01±1.1
3	18.01±1.0
4	42.18±0.9
5	49.60±1.0
6	64.82±0.75
7	79.67±1.06
8	80.12±1.48

Histopathology of buccal mucosa membrane

The success of mucoadhesive buccal drug delivery system is depends on safety of a drug on its site of application. Therefore histopathological study of mucoadhesive pantoprazole tablet was performed according to guidelines and approval provided by provided by Institutional Animal Ethical Committee (IAEC) - (MCP/IAEC/39/2011) of Modern College of Pharmacy, Nigdi, Pune. The histopathological study confirmed the safety of mucoadhesive pantoprazole tablet when it was kept for 24 h at site of application. The section of mucosa treated with mucoadhesive pantoprazole tablet showed no degeneration of buccal epithelium. There was no sign of remarkable destructive effect of formulations on the treated buccal mucosa. Photographs of mucosa were shown in the Fig.4. The results indicate that safety of prepared formulation.

CONCLUSION

It is concluded that magnesium oxide stabilize the pantoprazole buccal adhesive tablet composed of pantoprazole-sodium alginate-HPMC K4M-magnesium oxide, without collapse and stabilize a tablet in human saliva for at least 6 h. Buccal adhesive tablet could be attached on human cheek depends on combination of mucoadhesive polymer Sodium alginate and HPMC K4M concentration. Pantoprazole mucoadhesive tablet gave sustain release as well as good mucosal diffusion of pantoprazole. Our results suggest that pantoprazole buccal adhesive tablet would be

useful to deliver pantoprazole which degrades very rapidly in acidic aqueous medium and undergoes hepatic first pass metabolism following oral administration. It could be improve bioavailability of pantoprazole. The *in vitro* release kinetics studies reveal that all formulations fits well with zero order kinetics followed by Korsmeyer-Peppas, and Hix.Crow.s model and the mechanism of drug release is non-Fickian diffusion. Further, *in vitro* drug diffusion study is to be carried out for the best formulation using sheep mucosa.

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