Formulation and Evaluation of Mucoadhesive Buccal Films of Esomeprazole Magnesium Trihydrate

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ABSTRACT

The purpose of this study was to develop formulation and systematically evaluate *in vitro* performances of mucoadhesive patches of Esomeprazole magnesium trihydrate using HPMC K4M, HPMC (15cps), and HPMC (5cps) for avoiding gastric degradation and prolong the release up to 8 h. The films were smooth and elegant in appearance, uniform in thickness, weight, drug content and good folding endurance. Drug and polymer incompatibility was not shown in FTIR study. *In-vitro* release studies were reveal that all films exhibited sustained release in range of 87.31 to 98.04% for a period of 8 h. *Ex-vivo* permeation studies of Esomeprazole magnesium trihydrate were shown in the range of 84.35 to 91.33%.The best mucoadhesive performance and prolonged release was exhibited by formulation F_2. Formulation F_2 was shown 91.45% drug release after 8 h and 28.4 gm mucoadhesive force. It was followed zero order drug release pattern and non-fickian release behavior. Therefore, buccal patches containing HPMC K4M (3%) was shown satisfactorily results for alternative route of administration of Esomeprazole magnesium trihydrate for avoiding gastric degradation and sustain release.

Keywords: Esomeprazole magnesium trihydrate, Buccal patches, *In-vitro* drug release, *Ex-vivo* permeation.

INTRODUCTION

In recent years, buccal route of drug delivery offers distinct advantage over oral drug delivery to avoid pre-systemic metabolism or instability in the acidic environment of therapeutic agents.[1] Moreover, buccal drug absorption can be promptly terminated in case of toxicity by removing the dosage form from the buccal cavity.[2] In general, dosage forms designed for buccal administration should not cause irritation and should be small and flexible enough to be accepted by the patient. Buccal patches are highly flexible and thus much more readily tolerated by the patient than tablets. Buccal patches also ensure more accurate dosing of the drugs as compared to gels and ointments in oral cavity.[3,4]

Esomeprazole magnesium trihydrate is a proton pump inhibitors and is approved by FDA for the treatment of symptomatic gastroesophageal reflux disease, short-term treatment and maintenance of erosive esophagitis. The bioavailability of Esomeprazole magnesium trihydrate is 48% and plasma elimination half life is 1–1.5 h. Additionally, problems of Esomeprazole magnesium trihydrate such as high first pass metabolism and drug degradation in the harsh gastrointestinal environment can be circumvented by administering the drug via the buccal route.[5]

In view of these facts, this drug can be considered as a suitable candidate for buccal drug delivery. The purpose of this study was to develop formulations and systematically evaluate *in vitro* performances of buccoadhesive patches of Esomeprazole magnesium trihydrate using different grades of hydroxy propyl methylcellulose (HPMC (5cps), HPMC K4M and HPMC (15cps)) as base matrix. The *in-vitro* release characteristics of the prepared patches were evaluated using USP type II dissolution apparatus, the

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adhesion measurement was conducted using modified balance test, and *ex-vivo* permeation was conducted with chicken pouch mucosa.

MATERIALS AND METHODS

Materials

Esomeprazole magnesium trihydrate was obtained from Cipla Pvt. Ltd. as a gift sample (Mumbai, India). HPMC (5cps), HPMC-K4M and Polyethylene glycol were obtained from High Purity Laboratory Chemical, Mumbai. HPMC (15cps) was obtained from ACS Chemicals, Ahmedabad. Methanol was obtained from Sisco Research Laboratory Pvt. Ltd, Mumbai. Chicken pouch was obtained from Slaughter House, BSF, Gandhinagar. Double distilled water was prepared in laboratory for study.

Methods

Preparation of buccal patches

Films were prepared by the solvent casting method using various grades and amount of HPMC as film forming polymers. The polymeric solutions were kept for swelling in water. Esomeprazole magnesium trihydrate was dissolved in ethanol, and the solution was added to polymer solutions and mixed thoroughly with magnetic stirrer using 300 rpm (Remi, India). Polyethylene glycol-400 (30% w/v) was added in drug-polymer mixture as plasticizer. Finally, thick solution was casted in petridish and inverted funnel was placed over it to avoid sudden evaporation. Films were dried at room temperature for 12 h. After drying, removed the films from the petridish and stored in desiccators till the evaluation tests were performed.[4] HPMC K4M, HPMC (15cps), and HPMC (5cps) were used to prepare buccal patches with different concentrations (Table 1). The diameter of petridish was 9 cm. therefore, total 318 mg drug has been incorporated to load 20 mg drug in 4 cm^2 area of buccal patch.

Physical characteristics of the patches

Physical appearance and surface texture of films

This parameter was checked simply with visual inspection of films and evaluation of texture by feel or touch.[3]

Weight uniformity and thickness of films

Three films of the size 4 cm^2 were weighed individually using digital balance (Reputed Micro System, India).[6,7] Thickness of the films was measured using screw gauge with a least count of 0.01 mm at different spots of the patches. The thickness was measured at three different spots of the films. The experiments were performed in triplicate.

Folding endurance of films

The flexibility of films can be measured quantitatively in terms of what is known as folding endurance.[8] Folding endurance of the films was determined by repeatedly folding (10 mm films) at the same place till it broke. The number of folding at the same place, without breaking gives the value of folding endurance. The experiments were performed in triplicate.

Swelling index of films

The swelling index of the films was determined by immersing pre-weighed patch of size 10 mm in 50 ml water. The films were taken out carefully at 5, 10 up to 30 m intervals, blotted with filter paper and weighed accurately.[9] The swelling index was calculated using following equation,

$$\% \text{ Swelling Index} = \frac{\text{Wet weight} - \text{Dry weight}}{\text{Dry weight}} \times 100$$

Surface pH of films

Surface pH was determined by the method similar to that used by Viram PJ *et al*.[10] Films were allowed in contact with 1 ml of distilled water (pH 6.5 ± 0.05) for sufficient period at room temperature. The surface pH was noted by bringing a combined glass electrode or pH

Table 1: Formulation of Esomeprazole Magnesium Trihydrate Loaded Buccal Films

Ingredients	Formulations									
	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10
Esomeprazole (mg)	318	318	318	318	318	318	318	318	318	318
HPMC-K4M (mg)	600	900	1200	–	–	–	–	–	–	–
HPMC-15cps (mg)	–	–	–	600	900	1200	–	–	–	–
HPMC-5cps (mg)	–	–	–	–	–	–	600	900	1200	1500
Ethanol (ml)	20	20	20	20	20	20	20	20	20	20
PEG-400 (ml)	0.18	0.27	0.36	0.18	0.27	0.36	0.18	0.27	0.36	0.45
Water (ml)	10	10	10	10	10	10	10	10	10	10

paper near the surface of patches and allowing equilibrate for 1 m. The experiments were run in triplicate.

Tensile strength

Tensile strength of the patch was determined with digital tensile strength tester (Tinius-Olsen, India).[11] The sensitivity range of the machine was 1-10 Newton's. It consists of two load cell grips. The lower one was fixed and upper one was movable. The test patch of size (1 × 4 cm^2) was fixed between these cell grips and force was applied till it breaks. The tensile strength of the patch was directly taken from the dial reading in Newton's, which was converted into kilogram.

$$\text{Tensile strength} = \frac{\text{Force at break}}{\text{Initial cross sectional area of the sample } (cm^2)}$$

Drug content

The patches were tested for drug content uniformity by UV-Spectrophotometric method.[12] Patches of 4 cm^2 were cut from three different places from the casted patches. Each patch was placed in 10 ml volumetric flask and dissolved in pH 6.8 phosphate buffer and 0.1 ml solution is taken and diluted with pH 6.8 phosphate buffer up to 10 ml (100 times dilution). The absorbance of the solution was measured at 301 nm using UV/visible spectrophotometer (Shimadzu UV-1700, Japan). The percentage drug content was determined using the standard graph and the same procedure was repeated for three patches.

In-vitro residence time

The *in-vitro* residence time was determined using disintegration apparatus (Electro lab, India).[13] The medium was 900 ml of pH 6.8 phosphate buffer maintained at 37 ± 2°C. The segments of sheep buccal mucosa was procured from local slaughter house, each of 3 cm length, were glued to the surface of a glass slab, which was then vertically attached to the apparatus. Each formulation were hydrated on one surface using pH 6.8 phosphate buffer and the hydrated surface was brought into contact with the mucosal membrane. The glass slab was vertically fixed to the apparatus and allowed to move up and down. The time required for complete erosion or detachment of the patch from the mucosal surface was recorded (n = 3).

Drug release studies

In-vitro release studies were carried out by rotating paddle method.[14] 200 ml of phosphate buffer (pH 6.8) was used as the dissolution medium, at 37.0 ± 0.5°C, and a rotation speed of 50 rpm was used. One side of the buccal patch was attached to the glass disk with instant adhesive (cyanoacrylate adhesive). The disk was put in the bottom of the dissolution vessel. Samples (5 ml) were withdrawn at predetermined time of interval and replaced with fresh medium. The samples were filtered through 0.45 µm Whatman filter paper and examined by using UV/visible spectrophotometer (Shimadzu UV-1700, Japan) at 301 nm. The average cumulative percentage drug release was determined.

Ex-vivo permeation study

Permeation studies were carried out using the modified Franz diffusion cell of internal diameter 2.5 cm with receptor volume of 20 ml.[14] Chicken pouch was procured from the local slaughter house. The buccal mucosa was excised and trimmed evenly from the sides and then washed in phosphate buffer pH 6.8 and used immediately. The membrane was stabilized before mounting in order to remove soluble components. The mucosa was mounted between the donor and receptor compartment. The donor compartment contained a solution of 3 ml of phosphate buffer pH 6.8 in which 20 mg of Esomeprazole magnesium trihydrate was dissolved. The receptor compartment was filled with 20 ml phosphate buffer pH 6.8. The entire set up was placed over magnetic stirrer and temperature was maintained at 37°C by placing the diffusion cell in a water bath.

Stability study

The purpose of stability testing was to provide evidence on how the quality of a drug substance or drug product varies with time under the influence of a variety of environmental factors. To assess the formulation stability, stability studies were done as per ICH guidelines.[15] Patches were placed in a glass beaker lined with aluminium foil and kept in a humidity chamber maintained at 40 ± 2°C and 75 ± 5% relative humidity for 1 month. Changes in the appearance, bioadhesion, *in-vitro* release and *ex-vivo* permeation and drug content of the stored patches were investigated at the end of every week. The data represented were the mean of three determinations.

RESULTS AND DISCUSSION

The weight of the patches was determined using digital balance and the weight uniformity of all patches was given in Table 2. The drug loaded patches were tested (4 cm^2) for uniformity of weight. The patches were found uniform in weight. The thickness of the patches was measured using screw gauge. The thickness of the patches prepared with F_2 (HPMC K4M 3%), F_5 (HPMC (15cps) 3%) and F_9 (HPMC (5cps) 4%) were found to be 0.125 mm, 0.132 mm, and 0.184 mm respectively. The folding endurance was measured manually by

Table 2: Physical Evaluation of Mucoadhesive Buccal Films

FC	Swelling index	Folding endurance	Weight uniformity (mg)	Thickness uniformity (mm)
F1	36.84 ± 0.658	292 ± 2.642	67 ± 0.365	0.092 ± 0.004
F2	41.97 ± 0.336	311 ± 1.365	69 ± 0.851	0.125 ± 0.005
F3	34.67 ± 1.083	285 ± 3.248	71 ± 0.845	0.165 ± 0.002
F4	37.25 ± 0.733	297 ± 2.478	95 ± 1.057	0.125 ± 0.016
F5	35.51 ± 0.597	314 ± 1.147	112 ± 0.982	0.132 ± 0.004
F6	40.15 ± 1.022	276 ± 4.265	128 ± 1.512	0.184 ± 0.003
F7	41.51 ± 0.321	285 ± 2.348	59 ± 0.856	0.143 ± 0.005
F8	38.46 ± 1.001	292 ± 1.235	63 ± 1.248	0.152 ± 0.004
F9	36.98 ± 0.921	309 ± 2.245	71 ± 0.956	0.184 ± 0.005
F10	32.39 ± 1.054	281 ± 1.345	83 ± 1.256	0.221 ± 0.003

*FC = Formulation Code.
Note: Values in parenthesis are standard deviation (±SD); n = 3.

folding the film repeatedly at a point until it broke. The breaking time was considered as the end point. The folding endurance test did not develop any visible cracks or breaks (>300 times), thus showing good film elasticity and exhibited good physical and mechanical properties (Table 2). Hydration is required for a mucoadhesive polymer to expand and create a proper macromolecular mesh of sufficient size and also to induce mobility in the polymer chains in order to enhance the interpenetration process between the polymer and mucin. Polymer swelling permits a mechanical entanglement by exposing the bioadhesive sites for hydrogen bonding and/or electrostatic interaction between the polymer and the mucus network.[10] The measurement of swelling index indicated that not more significant difference observed amongst various grades of HPMC for swelling behaviour (Table 2). Formulation F_2 (HPMC K4M, 3%) shown maximum swelling index (41.97%).

Considering the fact that acidic or alkaline pH may cause irritation to the buccal mucosa. Therefore, surface pH of the buccal patches was determined. The surface pH of the patches was determined in order to investigate the possibility of any side effects in the oral cavity. The surface pH of the patches was found to be in range of 6.146 ± 0.056 to 6.833 ± 0.109 (Table 3). The tensile strength of all the patches was evaluated by using tensile strength tester. F_3 (HPMC K4M 4%) was shown higher tensile strength. It was shown that tensile strength increased with increase in the polymer content. Similar pattern was observed in formulations with polymers HPMC (5cps) and HPMC (15cps) (Table 3). Esomeprazole magnesium trihydrate buccal films prepared with various polymers were subjected to the evaluation for uniform dispersion of drug throughout the patch. The drug was dispersed in the range of 88.56 to 98.98% suggesting that drug was uniformly dispersed throughout all prepared films (Table 3).

Figure 1 shows the effect of bioadhesive polymers on the *in vitro* adhesion time of the different Esomeprazole films. It was observed that the bioadhesive polymers predominantly increased the *in-vitro* adhesion time of film. HPMC a is long-chain, non-ionic polymer and its adhesion property may be due to the formation of physical or hydrogen bond with mucus components of

Table 3: Physical Evaluation of Mucoadhesive Buccal Films

FC	Surface pH	Tensile strength (kg/cm²)	Drug content (%)	In vitro residence time (h)	Mucoadhesive strength (gm)
F1	6.486 ± 0.025	6.65 ± 0.065	91.96 ± 0.556	4.52 ± 0.215	19.95 ± 0.965
F2	6.833 ± 0.109	6.88 ± 0.406	98.98 ± 0.698	6.53 ± 1.024	28.4 ± 0.482
F3	6.543 ± 0.041	7.1 ± 0.776	92.49 ± 0.874	6.35 ± 0.651	27.95 ± 0.354
F4	6.480 ± 0.065	4.71 ± 0.374	93.41 ± 1.025	2.32 ± 0.985	17.8 ± 0.685
F5	6.146 ± 0.056	4.95 ± 0.610	97.39 ± 0.235	4.05 ± 0.965	22.15 ± 0.645
F6	6.236 ± 0.120	5.45 ± 0.585	92.49 ± 0.645	4.26 ± 1.056	26.45 ± 0.751
F7	6.403 ± 0.080	4.91 ± 0.512	88.58 ± 0.943	4.54 ± 0.568	14.8 ± 0.254
F8	6.476 ± 0.135	5.08 ± 0.311	95.35 ± 0.431	5.12 ± 1.085	17.35 ± 0.485
F9	6.323 ± 0.070	5.37 ± 0.153	98.91 ± 0.874	5.47 ± 0.965	22.7 ± 0.265
F10	6.453 ± 0.130	5.84 ± 0.270	92.14 ± 0.812	5.53 ± 0.684	23.47 ± 0.257

*FC = Formulation Code.
Note: Values in parenthesis are standard deviation (±SD); n = 3.

the tissue used. In case of HPMC K4M, formulation F_2 and F_3 were produced more bioadhesion compare to HPMC (5cps) and HPMC (15cps) formulations. These could be explained on basis of viscosity, in case HPMC K4M (3000–4000 mPa.s) has higher viscosity compare to another grades used. Higher in vitro adhesion time was shown by HPMC K4M (F_1–F_3) might be resulted from its higher viscosity and molecular weight.[12] Similar pattern for *in vitro* adhesion time was found for HPMC (15cps) and HPMC (5cps) prepared patches. Higher residence time was shown in an order F2 > F10 > F6.

Figures (2–4) shows the release profile of Esomeprazole magnesium trihydrate from different mucoadhesive

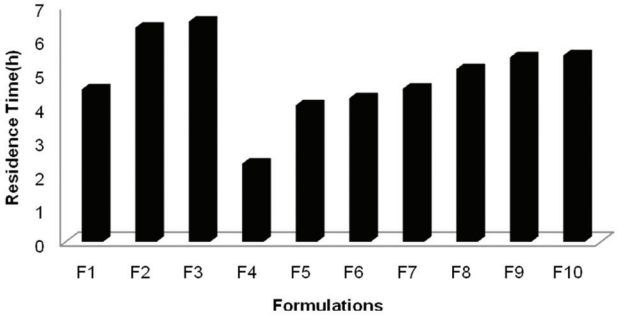

Figure 1: *In vitro* residence time for F1–F10 buccal patch formulations.

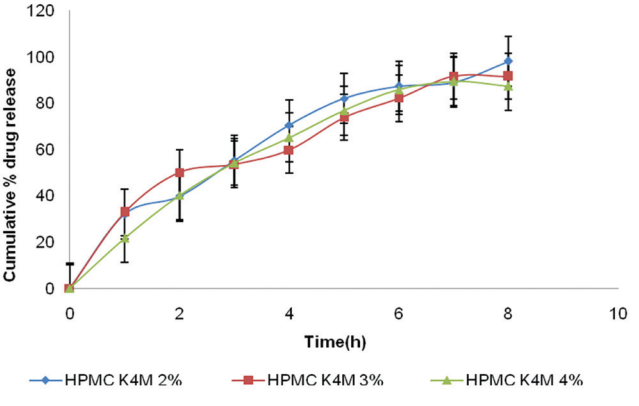

Figure 2: Release profiles of Esomeprazole from patches F1–F3 at 37°C and pH 6.8 (n = 3).

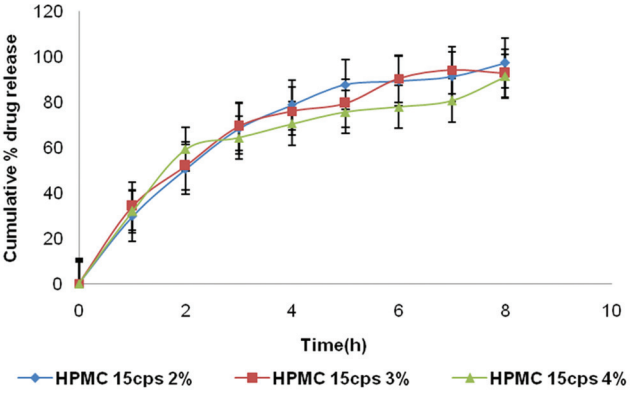

Figure 3: Release profiles of Esomeprazole from patches F4–F6 at 37°C and pH 6.8 (n = 3).

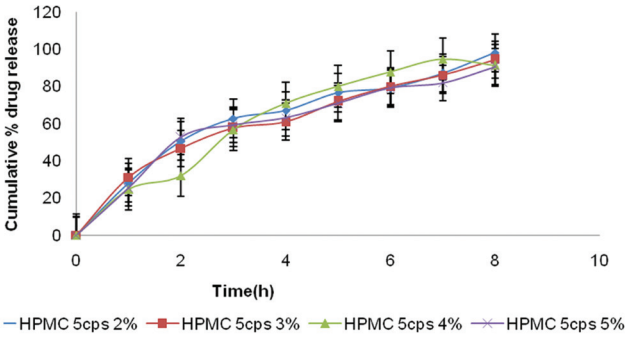

Figure 4: Release profiles of Esomeprazole from patches F7–F10 at 37°C and pH 6.8 (n = 3).

films. The release of Esomeprazole magnesium trihydrate from buccal films was in the range of 21.60 to 34.15% and 90.46 to 98.01% at the end of 1 h and 8 h respectively. It can be clearly seen that in all patches the drug released decreased with time. This could be due to the extensive swelling of the polymers creating a thick gel barrier, thus making drug diffusion to be slower with time. Mean dissolution time (MDT) reflects the time for the drug to dissolve and is the first statistical moment for the cumulative dissolution process that provides an accurate drug release rate. It is accurate expression for drug release rate. A higher MDT value indicates greater drug retarding ability. Higher MDT value for HPMC K4M (3%) is 1.64. MDT values of buccal patches prepared with HPMC (5cps) and HPMC (15cps) are lower than that of HPMC K4M. Additionally, formulation F_2 was indicated 6 h for 80% drug release from buccal patch (Table 5). It was found that residence time of drug varied with respect to proportion of polymers.[14] Formulations containing HPMC (15cps), and HPMC (5cps) were not given more than 5 h residence time even though drug release was more than 90%. Therefore, less residence time was not acceptable for buccal formulation for therapeutic efficacy. In case of HPMC K4M, formulation F_2 and F_3 had better residence time with optimum drug release up to 8 h.

The *in-vitro* drug release data was fit into first order, zero order, hixon-crowell, korsmeyer-peppas and Higuchi release kinetics. The optimized formula F_2 was followed zero order drug release kinetic. To understand the mechanism of release of Esomeprazole magnesium trihydrate from the patches the drug release data was fit into the hixon-crowell and Higuchi's models. The better fit (highest r^2 values) was observed in case of hixon-crowell model than Higuchi's model. Hence mechanisms of drug release from the patches were followed dissolution controlled.[14] It follows non-fickian diffusion mechanism (Table 4).

Ex-vivo drug permeation study was performed for all the prepared formulations without addition of penetration

Table 4: Kinetic Data of Esomeprazole Magnesium Trihydrate Mucoadhesive Buccal Films

FC	Higuchi	Zero order	Korsmeyer-peppas	Hixon-crowell	First order	n-value
F1	0.9819	0.9634	0.964	0.9634	0.9434	0.552
F2	0.985	0.9974	0.9842	0.9974	0.9845	0.5357
F3	0.9927	0.972	0.9922	0.972	0.9241	0.7079
F4	0.9733	0.9359	0.9808	0.9359	0.8934	0.5609
F5	0.9891	0.9623	0.993	0.9624	0.9258	0.5076
F6	0.9841	0.9578	0.9876	0.9578	0.9225	0.33
F7	0.979	0.9957	0.9624	0.9957	0.9949	0.3306
F8	0.9903	0.9934	0.9851	0.9934	0.9909	0.4127
F9	0.9843	0.9699	0.9818	0.97	0.9421	0.7176
F10	0.9952	0.9966	0.9862	0.9966	0.9876	0.3571

Table 5: Similarity Factor (f_2), Mean Dissolution Time (MDT), Time to Dissolve 80% Drug ($t_{80\%}$) and Flux for Buccal Films

FC	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10
f_2	88.72	96.70	95.81	75.32	86.51	88.76	89.66	93.49	93.35	93.04
MDT	1.60	1.64	1.63	1.32	1.41	1.26	1.52	1.57	1.48	1.48
$T_{80\%}$ (hrs)	4.5	6.00	5.21	4.18	5.02	7.06	6.07	6.01	5.02	6.23
Flux	2.26	2.15	2.50	2.13	2.13	1.48	1.74	1.96	2.77	1.50

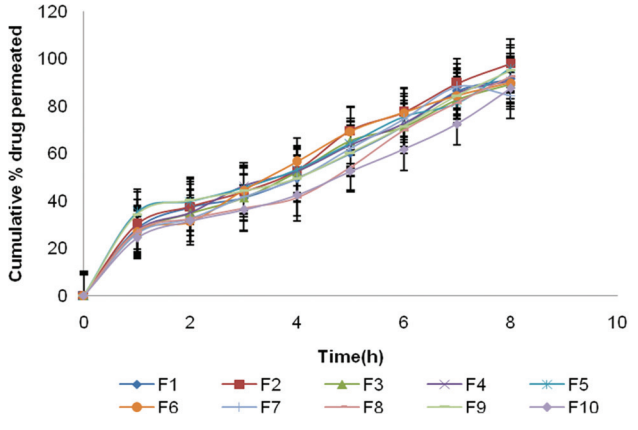

Figure 5: Release profiles of Esomeprazole from patches F1–F10 in Franz diffusion cell at 37°C and pH 6.8 (n = 3).

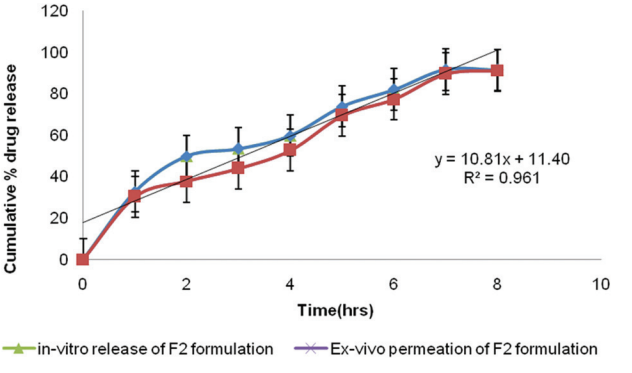

Figure 6: *In-vitro* release and *Ex-vivo* permeation study of formulation F_2.

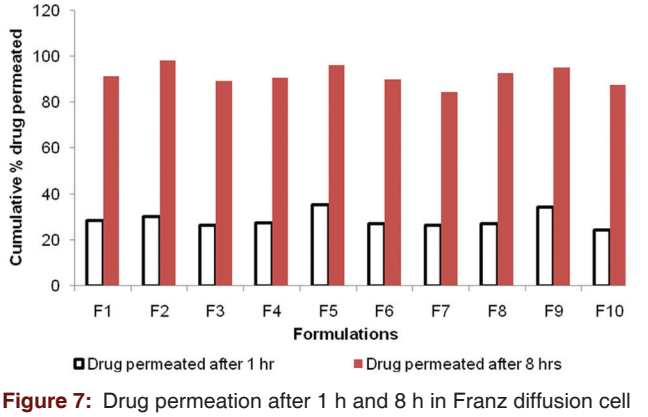

Figure 7: Drug permeation after 1 h and 8 h in Franz diffusion cell at 37°C and pH 6.8 (n = 3).

enhancers (Figure 5). Permeation of drug through mucosa from buccal patches was in the range of 84.35 to 97.91% at the end of 8 h respectively. It was found that formulation F_2 showed good swelling, a convenient residence time as well as promising drug release pattern.[14] *In vitro* release profile and theoretical release profile (not shown here) were compared *ex vivo* release profile for similarity. f_2 values for *ex-vivo* permeation profile with *in-vitro* release profile and theoretical drug release profile were found to be 93.98 and 97.75 respectively. *In-vitro* release profile and *ex-vivo* permeation profile of F_2 formulation was found to be superimposible (Figure 6). The coefficient correlation for batch F_2 was found to be 0.961 in satisfactory manner and showings sustain diffusion of drug through buccal permeation. Also, flux value (2.15) was satisfactory for F_2 formulation.

The FTIR spectra of all samples are shown in Figure 8. In the infrared spectrum of Esomeprazole magnesium trihydrate in combination of HPMC K4M, the 1575 cm^{-1} peak assigned to C = C stretching of aromatic

Table 6: Results of Stability Study

Time	1st week	2nd week	3rd week	4th week
% Drug content	98.52 ± 0.057	98.13 ± 0.348	97.26 ± 0.091	96.95 ± 0.054
Appearance	No changed	No changed	No changed	No changed
Mucoadhesive strength	28.12 ± 0.279	28.04 ± 0.457	27.98 ± 0.169	27.74 ± 0.158
Drug released after 8 h	91.14 ± 0.151	90.98 ± 0.057	90.43 ± 0.026	90.03 ± 0.254
Drug permeated after 8 h	91.03 ± 0.085	90.75 ± 0.241	90.17 ± 0.057	89.75 ± 0.425

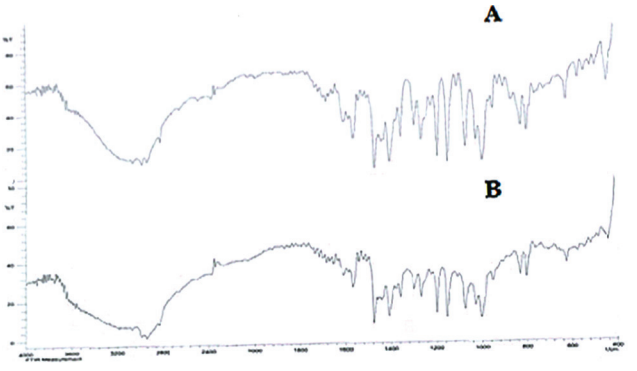

Figure 8: FTIR Spectra of Esomeprazole Magnesium Trihydrate (A) and Esomeprazole Magnesium Trihydrate with HPMC K4M (B).

ring, the 1100 cm^{-1} peak assigned to S = 0 stretching, and 2970 cm^{-1} peak assigned to C-H stretching of CH_3 group. The IR spectra of the patch showed the same absorption bands, illustrating absence of interaction between Esomeprazole magnesium trihydrate and HPMC K4M. It presumably suggests that the drug molecule is present in an unchanged state in the patch. The stability studies were carried out on the most satisfactory formulations F_2. There was no significant difference in appearance, drug content, mucoadhesive strength, drug release and permeation after 8 h (Table 6).

CONCLUSION

Development of bioadhesive buccal drug delivery of Esomeprazole magnesium trihydrate patches was one of the alternative route of administration to avoid acid degradation and to provide controlled release. Esomeprazole magnesium trihydrate buccal patches were prepared by solvent casting technique using HPMC (5cps), HPMC (15cps), and HPMC K4M and patches were evaluated for several of parameters. Formulation F_2 exhibited good physical appearance, better mechanical strength with acceptable flexibility. *In vitro* drug release and *ex vivo* permeation results were super impossible for films of HPMC K4M (3%). From stability study, formulation F_2 was shown good bioadhesion, promising drug release and satisfactory permeation. Hence, it was concluded that, 3% HPMC K4M and 30% w/v plasticizer was required for better physico-chemical and mechanical property of Esomeprazole magnesium trihydrate loaded buccal patch using solvent casting technique.

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