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Formulation and Evaluation of Enalapril Maleate Mucoadhesive Buccal Film

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ABSTRACT

Enalapril maleate is used in the treatment of hypertension and angina pectoris. It shows low bioavailability due to high hepatic first pass metabolism. Hence the present work was undertaken to formulate mucoadhesive buccal films of enalapril maleate with an objective to improve therapeutic efficacy, patient compliance and the bioavailability. In the present study ten formulations of mucoadhesive drug delivery system of enalapril maleate were prepared as buccal films, by solvent casting technique. Hydroxy propyl methyl cellulose,methyl cellulose combination of both were used as mucoadhesive polymers. Prepared films were evaluated for their weight, thickness, surface pH, swelling index, drug content uniformity, *in vitro* residence .time, folding endurance *in vitro* release and permeation studies. Films exhibited controlled release over more than 10 h in permeation studies. It was concluded that the films containing 20 mg of enalapril maleate inhydroxy propyl methylcellulose and methyl cellulose 1% w/v , (F9&F10) showed good swelling, a convenient residence time and promising controlled drug release, thus can be selected for the development of buccal film for effective therapeutic uses.

Keywords: Enalapril maleate,buccal film,mucoadhesive buccal film, *invivo* studies.

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INTRODUCTION

Among the various routes of administration oral route is the most convenient, easy and preferred one. However, orally administered drugs are either prone to hepatic first-pass metabolism or metabolism in gastrointestinal (GI) tract or both. These are the main reasons for which some classes of drugs like peptides and proteins cannot be administered orally. Delivery of drugs through various mucosal surfaces (nasal, rectal, vaginal, ocular and oral mucosa) may form the potential alternative solution for delivery of such classes of drugs. These mucoadhesive drug delivery systems improve the bioavailability of the drugs by bypassing the first pass effects and avoiding the presystemic elimination of the drug within the GI tract[1]. Out of the various sites available for mucoadhesive drug delivery, buccal mucosa is the most suited one for local as well as systemic delivery of drugs. It's anatomical and physiological features like presence of smooth muscles with high vascular perfusion, avoidance of hepatic first pass metabolism and hence can potentially improve bioavailability are the unique features which make it as an ideal route for The drug dissolution (release) and permeation through the mucosa are governed by microenvironment of the mucosa. The microenvironment of the mucosa can be adjusted or modified with the help of well-designed mucoadhesive drug delivery systems[2]. These systems are designed and formulated with the help of mucoadhesive polymers which are generally of high molecular weight and of high viscosity grades with greater flexibility and optimum chain length. Various mucoadhesive polymers have also been investigated for buccal drug delivery[3-5]. Among the various mucoadhesive drug delivery systems, buccal films are better than oral gels and buccal tablets due to relatively longer residence time, more flexibility to cover the buccal mucosa and better comfort. Enalapril maleate is an angiotensin converting enzyme (ACE) inhibitor, used mainly in the treatment of hypertension and angina Pectoris. It has low bioavailability (40-60%) due to hepatic first pass metabolism[6]. Hence to improve its therapeutic efficacy and bioavailability the drug may be administered by buccal route through buccal films. Buccal delivery of enalapril maleate may circumvent hepatic first pass metabolism and improve bioavailability. Hence the present work deals with the formulation and characterization of mucoadhesive buccal film of enalapril maleate using mucoadhesive polymerhydroxyl propyl methyl cellulose (HPMC), methylcellulose (MC) and combination of both (HPMC&MC).

MATERIALS AND METHOD

Enalapril Maleate was a gift sample (Intas Pharmaceutical Ltd. Dehradun), and HPMC (47 centipoise), MC (high viscosity grade) were obtained from Research-Lab Fine Industries. Other chemicals used were of analytical grade. The film were prepared by solvent casting method.

Preparation of mucoadhesive buccal films:

Buccal films of enalapril maleate were prepared by solvent casting technique using film forming mucoadhesive polymers (Table 1). HPMC was weighed (20 mg) accurately and dissolved in 2 ml of ethanol. The beaker containing polymer and ethanol was kept aside for 5 min for swelling of the polymer. Further 3 ml of ethanol was added to the above polymer solution and the dispersion was stirred. Then one drop of (0.029 g) propylene glycol was added to the polymer solution. Simultaneously enalapril maleate was accurately weighed in quantity such that 1 cm^2film contained 20 mg and then dissolved in 5 ml of ethanol in another beaker. The drug solution was added to the polymer solution and was mixed thoroughly with the help of a magnetic stirrer. The whole solution was poured into the glass Petri dish placed over a flat surface. Inverted funnel was placed over the dish to avoid sudden evaporation. The moulds containing polymeric solution of drug was kept 12 hours at room temperature for drying. After drying, the films were observed and checked for possible imperfections upon their removal from the moulds.

They were covered with wax paper and preserved in desiccators till the evaluation tests were performed. These new films were examined in order to select the film having the best characteristics. Similarly, film of F1 were prepared.

For preparing films F2, F3,F4 different ratios of HPMC polymer and drug was placed in ethanol and stirred for 1 h. the solution were mixed and poured in to Petri dish. For F5, F6, F7, F8different ratios of MC polymer and drug was placed in ethanol and stirred for 1 h. the solution were mixed and poured in to Petri dish. F9&F10 combination of both polymers different ratios of HPMC&MC drug was placed in Ethanol and stirred for 1hour.The Petri dishes containing polymeric solutions of drug were kept aside for 12 hours at room temperature for drying. The dried films were cut into size of 2 cm diameter, packed in aluminum foil and stored in a desiccator until further used.

Table 1: Formulation and Preparation of Buccal Films

Ingredients	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10
Drug (mg)	20	20	20	20	20	20	20	20	20	20
HPMC K15M (mg)	250	500	750	1000	-	-	-	-	-	-
Methyl cellulose (mg)	-	-	-	-	250	500	750	1000	-	-
HPMCK15M&MC (mg)	-	-	-	-	-	-	-	-	250 250	750 250
Propylene glycol (ml)	0.24	0.24	0.24	0.24	0.24	0.24	0.24	0.24	0.24	0.24
Ethanol (ml)	5	10	15	20	5	10	15	20	20	20

Characterization of mucoadhesive buccal films:

Three films of every formulation were weighed individually in a digital balance (Fisher Brand PS-200) and the mean weights were calculated. The mean value of film thickness was calculated by

measuring thickness of three films of each formulation at three different places using Micrometer Screw Gauge (Mitutoyo MMO-25DS).

Folding endurance:

Folding endurance was determined by repeatedly folding a small strip of size (2×2 cm) of film at the same place till it broke. The mean value (three readings and standard deviation) of folding endurance (the number of times, the film could be folded at the same place without breaking) were shown in (Table 2).

Table: 2 Physicochemical Properties of Enalapril Maleate Mucoadhesive Buccal Film

S.No	Formulation code	Swelling index with drug	Folding endurance	Surface PH	Content uniformity	*In vitro* residence time (hr)	Mean thickness (mm)±SD
1	F1	17.12±1.14	234.4±6.47	6.23±0.02	19.0±0.01	2.23±0.56	0.17±0.03
2	F2	20.24±1.15	222.5±10.31	6.51±0.02	17.7±0.01	3.01±0.72	0.15±0.01
3	F3	21.33±1.11	279.0±8.02	6.72±0.05	17.8±0.01	1.87±0.09	0.15±0.02
4	F4	25.34±1.21	178.5±4.62	6.64±0.08	18.3±0.01	4.00±0.09	0.22±0.01
5	F5	31.01±0.22	257.0±5.11	6.35±0.09	18.2±0.01	2.33±0.55	0.16±0.02
6	F6	43.11±0.30	187.5±8.12	6.22±0.10	21.0±0.01	2.99±0.70	0.18±0.03
7	F7	28.03±0.33	165.5±12.22	6.31±0.01	19.5±0.02	1.88±0.92	0.21±0.01
8	F8	31.81±0.23	277.0±3.39	6.65±0.02	18.8±0.01	3.87±0.08	0.17±0.03
9	F9	46.28±0.32	287.0±5.02	6.67±0.02	20.0±0.01	4.11±0.09	0.17±0.01
10	F10	46.83±1.22	245.4±9.65	6.45±0.02	19.4±0.01	1.75±0.07	0.16±0.02

Drug content:

To determine the drug content uniformity, three film units of each formulation were taken in separate 100 ml volumetric flasks, 100 ml of pH 6.8 phosphate buffer was added and continuously stirred for 24 hours. The solutions were filtered, diluted suitably and analyzed at 267 nm in a UV spectrophotometer (Lambda 25, Perkin Elmer, US). The average of drug contents of three films was taken as final reading.

Surface pH:

To determine surface pH of films, buccal films were left to swell for 1 hour on the surface of the agar plate, prepared by dissolving 2% (w/v) agar in warmed isotonic phosphate buffer of pH 6.6 under stirring and then poured the solution into the Petri dish allowed to stand till gelling at room temperature. The surface pH was measured by means of pH paper placed on the surface of the swollen film.

Swelling index:

For studying swelling properties, a drug-loaded film of 10×10 $mm^2$was weighed on a pre-weighed cover slip. It was kept in a Petri dish and 50 ml of pH 6.6 phosphate buffer was added. After every five min, the cover slip was removed and weighed up to 30 min. The difference in the weights gives

the weight increase due to absorption of water and swelling of film. The percent swelling, % S, was calculated using the following equation: percent swelling (% S)=(Xt-Xo/Xo)×100, where Xt is the weight of the swollen film after time t, Xo is the initial film weight at zero time[7].

***In vitro* residence time:**

The *in vitro* residence time was determined using IP disintegration apparatus using pH 6.6 phosphate buffer (PB) as the disintegration medium (800 ml, maintained at 37±2^{o}). On the surface of a glass slab the segments of rat intestinal mucosa (each of 3 cm length) were glued and then the slab was vertically attached to the apparatus. Three films of each formulation were hydrated (on one surface using pH 6.6 PB) 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 fi lm was completely immersed in the buffer solution at the lowest point and was out at the highest point. The time required for complete erosion or detachment of the fi lm from the mucosal surface was recorded (n=3) as given in (Table 2).

For the *in vitro* release study the USP XXIV six station dissolution apparatus type 1 (DA-6DR, Veego Ltd., India) with 900 ml pH 6.6 PB (dissolution medium) was used. One film of each formulation was fixed to the central shaft using a cyanoacrylate adhesive. During the release study the temperature and rotation speed of the apparatus was maintained at 37±0.5^{0} and 50 rpm, respectively. The release study was carried out for 2 h. After every hour, samples were withdrawn from each station, filtered, diluted suitably and then analyzed spectrophotometrically at 213 nm.

The *ex vivo* permeation studies of mucoadhesive buccal films of enalapril through an excised layer of porcine buccal mucosa (washed in isotonic phosphate buffer (pH 6.6) after excising and trimming from the sides) were carried out using the modified Franz diffusion cell[7,8]. A 2.0 cm diameter film of each formulation under study was placed in intimate contact with the excised porcine buccal mucosa and the topside was covered with aluminum foil as a backing membrane. The contents of receptor compartment filled with 100 ml of pH 7.4 phosphate buffer (with a Teflon bead placed inside) were stirred with a magnetic stirrer and temperature of 37±1^{0} was maintained throughout the experiment. The samples were withdrawn at every hour, filtered, diluted suitably and then analyzed using UV spectrophotometer at 213 nm.

RESULTS AND DISCUSSION

Buccal films of enalapril maleate were prepared by solvent casting technique with the use of mucoadhesive polymers such as HPMC K15 M,MC and combination of both. The prepared films

were evaluated for different physicochemical tests such as weight variation, thickness, content uniformity, swelling index, surface pH, *in vitro* residence time, and *in vitro* drug release studies.

All the films showed uniform thickness throughout. The film thickness was observed to be in the range of 0.22±0.01 to 0.15±0.01 mm and average thickness found was about 0.208 mm. The weights of different formulation were found to be in the range of 0.41±0.01 mg to 0.46 ±0.01 mg. The acidic or alkaline pH may cause irritation to buccal mucosa and may affect the drug release and degree of hydration of polymers. Therefore the surface pH of buccal film was determined to optimize both drug release and mucoadhesion. The surface pH of all formulations was within 6.72±0.05 units of the neutral pH and hence no mucosal irritation were expected and ultimately achieve patient compliance.

Folding endurance was measured manually by folding the film repeatedly at a point till they broke. Films did not show any cracks even after folding for more than 289 times. Hence it was taken as the end point. The folding endurance was found to be in the range of 165.5±12.22 to 277±3.39. The values were found to be optimum to reveal good film properties. The results of content uniformity indicated that the drug was uniformly dispersed; the content was in range of 17.7 to 20.0 mg/cm^2.

It was observed that incorporation of drug induced significant reduction of the residence time of various formulations. As also reported by some previous studies, the enhanced erosion rate was observed with the non ionic polymers (HPMC and MC). It might be explained by the particle swelling leading to the development of internal swelling force by matrix and this in turn promotes disintegration and leaching of drug leaving behind a highly porous matrix[7,9,10]. The *in vitro* residence time of various formulations was in order of F10>F3>F7>F1>F5>F6>F2> F8>F4>F9. The *in vitro* residence time of the films were found to be optimum and therefore films exhibited good swelling and drug release properties.

As the drug was uniformly dispersed in the matrix of the polymer, a significantly good amount of drug was loaded in all the formulations. The drug content was found to be in the range of 2.67 (F10) to 2.55 (F2). The order of drug content was found to be F10>F3>F4>F5>F2>F6>>F1>F8>F9.

In vitro release studies of various formulations were performed using pH 6.8 phosphate buffer as dissolution medium. The drug concentration was determined spectrophotometrically at 267 nm. Significant difference was observed in the release pattern of enalapril maleate films containing MC, HPMC. It was observed that during dissolution, MC containing films swelled forming a gel layer on the exposed film surfaces[11,12]. The loosely bound polymer molecules in these films were readily eroded, allowing the easy release of enalapril maleate as compared to HPMC. After 6 hours the release was found to be in the range of 78.6 to 96.35%. The rank order of drug release after 6 hr was

found to be 75.76>75.70>74.97>74.79>65.37>65.34>62.02 >54.54>50.71>47.27% for formulation F1>F4>F3>F8>F7>F2> F5>F6>F9>F10, respectively.

It was also concluded that formulation F9 and F10(containing MC and HPMC) showed good swelling, a convenient residence time as well as promising drug release. On the basis of release pattern, swelling and residence time, F9 and F10 formulations were chosen for *ex vivo* study. In e*x vivo* study, drug permeation through the porcine buccal mucosa was determined for formulation F9 and F10(fig. 2). The drug permeation was found to be 82.48 % and 90.86 % in F9 and F10after 10 h. The drug permeation decreased in *ex vivo* study in comparison of *in vitro* release. This decrease in drug diffusion observed from *ex vivo* study compared to *in vitro*, may be due to the lesser permeability of porcine mucosa and also the presence of a backing membrane in the *ex vivo* study, which make the release unidirectional. The backing membrane restricting the contact of the film with the receptor fluid to one side alone slows down the water uptake, swelling and disruption of the matrix in turn releasing lesser amount of drug in specified time, compared to the one without the backing membrane. The correlation coefficient values were found to be 0.9852 and 0.9667 for F9 and F10, respectively showing good correlation. It may be concluded that the release kinetics followed zero order. The Higuchi Plots of F5 and F6 were found to be almost linear with correlation coefficient values of 0.9310 and 0.9748. This proves that the drug permeation followed the matrix diffusion process.

The results of all the physical characterization of all formulations (F1–F10) were found to be satisfactory. The results of the study show that therapeutic levels of enalapril can be delivered buccally. The present study concludes that these erodible mucoadhesive buccal films containing enalapril can be very promising for effective doses to systemic circulation. These may also The results of all the physical characterization of all formulations (F1-F10) were found to be satisfactory. The results of the study show that therapeutic levels of enalapril can be delivered buccally. The present study concludes that these erodible mucoadhesive buccal films containing enalapril can be very promising for effective doses to systemic circulation. These may also provide an added advantage of circumventing the hepatic first pass metabolism. Films exhibited controlled release over more than 2 h. It was concluded that the films containing 20 mg of enalapril maleate in methylcellulose 1% w/v and hydroxypropyl methylcellulose 3% w/v (formulation F9), showed good swelling, a convenient residence time and promising controlled drug release, thus can be selected for the development of buccal film for effective therapeutic uses. Further, the study may be extended for assessing the *in vivo* release and *in vitro-in vivo* correlation.

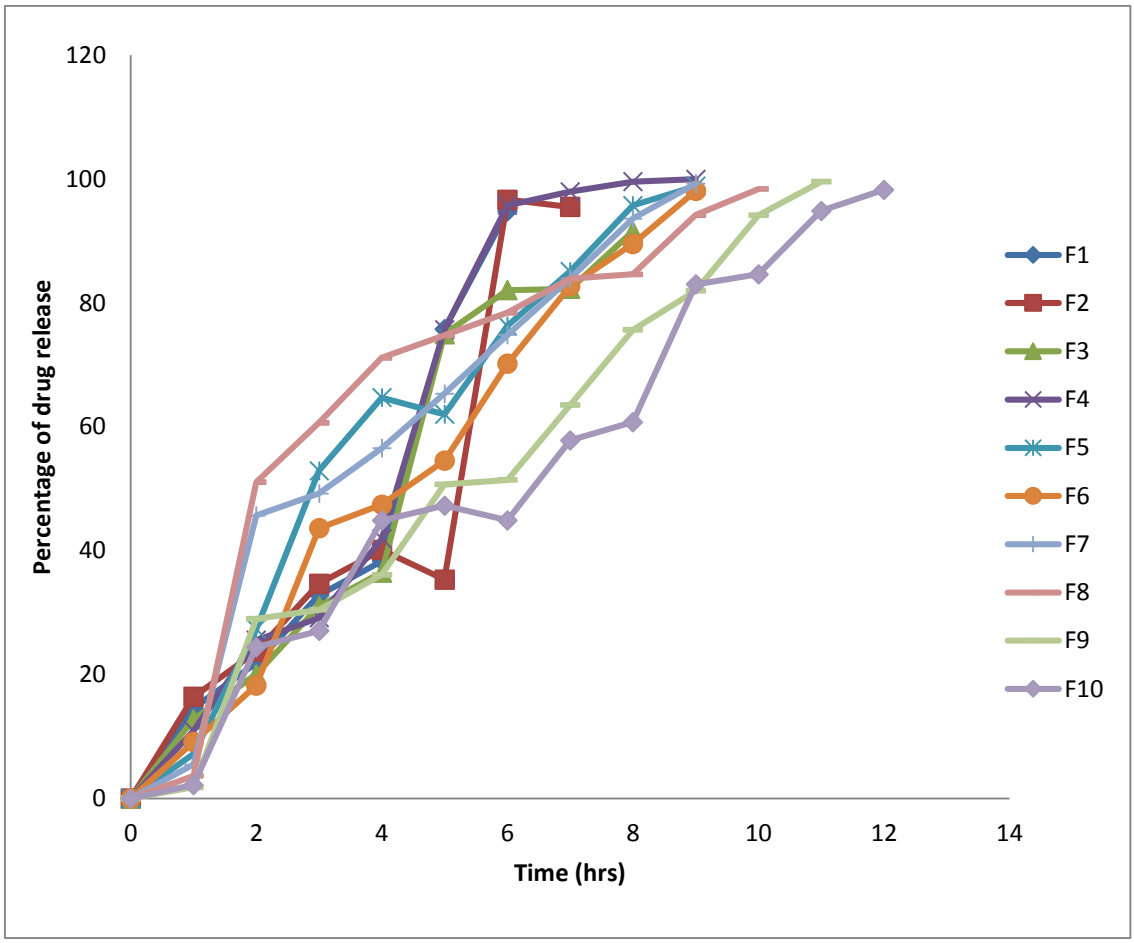

Figure 1: *In Vitro* Drug Release of Enalapril Maleate Mucoadhesive Buccal Film

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