ORIGINAL ARTICLE

Formulation Development of Olmesartan Medoxomil Mucoadhesive Buccal Film

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Abstract

Aim: Olmesartan medoxomil is an angiotensin II antagonist used in the management of hypertension. Mucoadhesive buccal films offer an attractive route of administration for systemic drug delivery through jugular vein leading to high bioavailability and greater therapeutic efficacy. **Materials and Methods:** Different formulations were carried out using natural polymer such as almond gum along with synthetic polymers. Formulations of F_1 to F_8 buccal films were prepared by solvent casting method by employing hydroxypropyl methylcellulose (HPMC) E50LV and almond gum alone, and in combination of HPMC E50LV and Eudragit RL100 and combination of HPMC E50LV and almond gum in different proportions. **Results and Discussion:** Buccal films were evaluated for their physicochemical characterization such as thickness, weight uniformity, folding endurance, drug content and surface pH, swelling index, percentage moisture loss, and uptake. **Conclusion:** Among all the formulations, F_7 was found to be satisfactory and surface pH of all films was found to be neutral. The *in vitro* release in optimized formulation F_7 was found to be 47.69% in 7 h, and drug release was found to be diffusion following first order as per kinetics ($R^2 = 0.9937$). Stability studies were carried out with selected formulations of F_7 and F_8.

Key words: Almond gum, Eudragit RL100, folding endurance, glycerin, hydroxypropyl methylcellulose E50LV, solvent casting technique, Tween 80

INTRODUCTION

Over the last two decades, throughout the world, there is an increasing demand from Pharmaceutical Companies for the development of buccal drug delivery techniques, with an estimated US market share of US$ 1208 million in 2020. It minimizes toxicity and improves efficacy, palatable, and patient compliance due to small size, dose, and thickness of buccal film over other dosage form.[1-4] Other advantages include excellent accessibility, low enzymatic activity, suitability for drugs or excipients that mildly and reversibly damage or irritate the mucosa, painless administration, easy withdrawal, facility to include permeation enhancer/enzyme inhibitor or pH modifier in the formulation, versatility in designing as multidirectional or unidirectional release system for local or systemic action. Buccal films provide satisfactory attachment with buccal layers, and hence it is most convenient and suitable dosage form as compared to others.[5-8]

Many researchers have explored natural polysaccharides such as gums and mucilages abundantly found in many higher plants have been extensively used for the development of dosage forms.[9,10] Mucilages are naturally occurring, high-molecular weight (approximately 200,000), and polyuronides consisting of sugar and uronic acid units.[11,12] Gums swell in water to form sticky, colloidal dispersions, and pectins gelatinize in water while mucilages form slippery, aqueous colloidal dispersions. Hence, the natural almond gums in low concentration were used for the preparation of buccal film, and hence such dosage forms are easy to handle,

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cost-effective, fast absorbable, non-irritating, elegant, and mostly preferred by consumer.[13,14]

Olmesartan medoxomil (OMX) is described chemically as the (5-methyl-2-oxo-1,3-dioxol-4-yl) methyl ester of 4-(1-hydroxy-1-methylethyl) -2-propyl-1-{[20-(1H-tetrazol-5-yl)[1,10- biphenyl]-4-yl]methyl}-1H-imidazole-5-carboxylic acid. It is a pro-drug and hydrolyzed to olmesartan during absorption from the gastrointestinal tract. It is an angiotensin antagonist (angiotensin receptor blockers).[8-11] It is a white crystalline powder and has limited solubility.

Although OMX has 100% oral absorption, due to high first-pass metabolism, it has a low and variable bioavailability. The drug is given in dose 20-80 mg twice a day, and hence there is less patient compliance. The physicochemical properties of OMX are slight water solubility and low molecular weight (558.585 g/mol). To overcome high first-pass metabolism, buccal patches were designed with an objective to increase its bioavailability which is a new route to develop a revolution in drug industry.[15,16]

Sustained release formulation was developed with polymers (Eudragit RL100), hydroxypropyl methyl cellulose (HPMC) E50LV, natural gum (almond gum) in various proportions which released the drug over an extended period of more than 12 h, giving an advantage of once a day dosing. Tween 80 was used as permeation enhancer and glycerin as plasticizer. Eudragit RL100 and HPMC are release-retardant mucoadhesive polymers with high swellability and hydrophilicity. Anionic polyelectrolytes like HPMC have been extensively used for designing mucoadhesive delivery systems due to their ability to exhibit strong hydrogen bonding with the mucin present in the mucosal layer.[17,18] Eudragit RL100 is a hydrophobic polymer with high mechanical strength. Hence, they will provide delayed release of drug from buccal patches for long time. Glycerin is used as an additive that increases the plasticity or fluidity of the formulation. Tween 80 modifies the solvent nature of stratum corneum, thus improving drug partitioning into skin and also increasing diffusivity of the drug into skin.[19,20]

MATERIALS AND METHODS

OMX was obtained as a gift sample from Astrazeneca, Bangalore, India. HPMC E50LV and Eudragit were obtained from Yarrow Chem, Products, Mumbai, whereas almond gum was procured from Arumuga Siddha Centre, Chennai.

Collection, purification, and identification of gum

The natural almond gum was collected from the local market available in Chennai. The almond gum was taken and well dried and powered in a motor and passed through sieve No. 100. Almond gum was soluble in distilled water and heated for some time and cooled. Then, the concentrated solution was precipitated in ethanol in ice-cold condition. The precipitate was separated and dried at 60°C. The dried gum was powdered and stored in tightly closed container. The characterization of gum is carried out by means of various tests for the identification of almond gum.[8]

Preformulation studies

The polymer and drug compatibility were checked by Fourier transform infrared (FTIR) analysis (Jasco FTIR 100) using potassium bromide discs to ensure there was no incompatibility. λ_{max} determination of OMX was done by ultraviolet (UV) spectroscopy using phosphate buffer pH 6.8 and a calibration curve of OMX was plotted by taking 2-18 µg/ml which was measured at 257 nm using phosphate buffer solution pH 6.8 as blank.

Preparation of OMX buccal film

The films containing OMX were prepared by solvent casting technique as shown in Table 1 using film-forming polymer

Table 1: Formulation of OMX

Ingredients	F_1	F_2	F_3	F_4	F_5	F_6	F_7	F_8
OMX (mg)	50	50	50	50	50	50	50	50
HPMC E50LV (mg)	400	300	250	200	-	300	250	200
Eudragit RL 100 (mg)	-	100	150	200	-	-	-	-
Almond gum (mg)	-	-	-	-	400	100	150	200
Glycerine (ml)	0.05	0.05	0.05	0.05	0.05	0.05	0.05	0.05
Ethanol (ml)	8-10	8-10	8-10	8-10	8-10	8-10	8-10	8-10
Acetone (ml)	-	10	10	10	10	10	10	10
Tween (ml)	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1
Water (ml)	-	-	-	-	3	3	3	3

HPMC: Hydroxypropyl methylcellulose, OMX: Olmesartan medoxomil

HPMC E50LV alone and in combination with Eudragit, almond gum using solvents such as ethanol (drug, HPMC, Eudragit, almond gum), acetone (Eudragit), and water. Tween 80 was used as solubilizing agent, and glycerin was used as plasticizer. Drug-polymer solution was prepared by stirring on magnetic stirrer and then films were casted in Petri plate (3 inch). The solvent was allowed to evaporate slowly by inverting funnel containing cotton in its stem. The films were allowed to dry at room temperature for 24-72 h, and then were packed in aluminum foil and stored in desiccator.[21]

Evaluation properties of OMX buccal films

Appearance[8]

The film was observed visually for their physical appearance and transparency. The film was examined for their surface texture such as smooth, rough, or very smooth.

Thickness[8]

The thickness of each patch is measured using digital vernier caliper at five different positions of the patch, and the average is calculated.

Average weight[21]

Five different randomly selected patches from each batch are weighed and the weight variation is calculated.

Drug content uniformity[22]

For drug content uniformity, a 3 cm patch (without backing membrane) is separately dissolved in 100 ml of ethanol and simulated saliva solution (pH 6.2) mixture (20:80) for 12 h under occasional shaking. The resultant solution is filtered and the drug content is estimated spectrophotometrically. The averages of three determinations are taken.

Surface pH[23]

The prepared buccal patches are left to swell for 2 h on the surface of an agar plate, prepared by dissolving 2% (w/v) agar in warm phosphate buffer of pH 6.8 under stirring and then pouring the solution into a Petri dish till gelling at room temperature. The surface pH is determined by placing pH paper on the surface of the swollen patch. The mean of three readings is recorded.

Folding endurance[23]

The folding endurance of each patch is determined by repeatedly folding the patch at the same place till it is broken or folded up to 300 times, which is considered satisfactory to reveal good film properties.

Swelling index (SI)[24,25]

Buccal patches are weighed individually (W_1) and placed separately in Petri dishes containing phosphate buffer pH 6.8. The patches are removed from the Petri dishes and excess surface water is removed using filter paper. The patches are reweighed (W_2) and SI is calculated as follows:

$$SI = (W_2 - W_1)/W_1$$

Moisture absorption and moisture loss[26]

The buccal patches are weighed accurately and kept in desiccator containing anhydrous calcium chloride. After 3 days, the patches are taken out and weighed. The moisture content (%) is determined by calculating moisture loss (%) using the formula as follows:

$$\text{Moisture content (\%)} = \text{Initial weight} - \text{Final weight}/\text{Final weight} \times 100$$

The buccal patches are weighed accurately and placed in a desiccator containing 100 ml of saturated solution of aluminum chloride, which maintains 76% and 86% relative humidity (RH). After 3 days, films are taken out and weighed. The moisture absorption is calculated using the formula as follows:

$$\text{Moisture absorption (\%)} = \text{Final weight} - \text{Initial weight}/\text{Initial weight} \times 100$$

In vitro dissolution study[26]

The drug release studies were performed with USP dissolution test apparatus (Paddle method). The USP dissolution apparatus was thermostated at the temperature of 37 ± 1°C and stirred at rate of 50 rpm. Each film was fixed on a glass slide with the help of cyanoacrylate adhesive so that the drug could be release only from upper face. Then, the slide has immersed in the vessel containing 500 ml of pH 6.8 phosphate buffer solution. The aliquots of 5 ml were withdrawn at the time interval of every hour and replaced with equal volume of dissolution medium for 6 h. The sink condition was maintained throughout the study. The samples were analyzed at 257 nm in UV-VIS Spectrometer and cumulative amount of drug release at various time intervals was calculated.

Release kinetics[27]

For determination of drug release kinetics from the buccal tablet, the *in vitro* release data were analyzed by zero order, first order, Higuchi and Korsmeyer and Peppas equations.

Stability studies[28]

Best formulation was stored in screw capped small glass bottles at room temperature and in stability chamber at 40 ± 1°C and 75% RH. Samples were analyzed for physical

appearance, residual drug content, and *in vitro* release after a period of 15, 30, and 45 days. Initial drug content was taken as 100% for each formulation.

RESULTS AND DISCUSSION

Pure OMX compound was examined for the solubility. It is insoluble in water and freely soluble in ethanol and alcohol. The OMX is highly soluble in methanol and ethanol and insoluble in water. Solubility studies were also performed in different buffer solutions to select the dissolution media which could maintain the sink conditions during in vitro release studies. The drug is slightly soluble in all buffers but has shown maximum solubility in pH 6.8 (0.0425 mg/ml) and was selected as a dissolution medium for *in vitro* dissolution study.

Preformulation studies on drug

OMX λ max was determined to be 257 nm. The calibration curve with concentration 2-18 µg/ml obeyed Beer's law is shown in Figure 1.

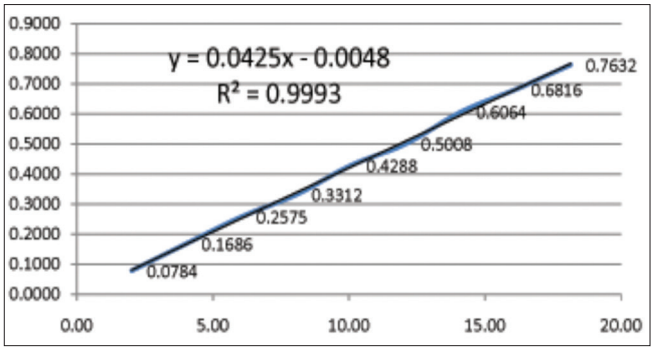

Figure 1: Standard calibration curve of olmesartan medoxomil

Infrared spectrum shows all prominent peaks of OMX. IR spectrum of pure OMX is shown in Figure 2; an absorption band was observed, peaks 2995.87/cm (C-H, str, Sp2), 2923.56/cm (C-H, str, Sp3), 1708/cm, 1832/cm (C-O, str) and 3300-3100/cm (N-H, str). These peaks can be considered as characteristic peaks of OMX and were not affected and prominently observed in IR spectra of OMX along with pure drug and mixture of drug and polymer, so there was no any chemical incompatibility between drug and polymers. Functional groups and their IR range of OMX, HPMC, Eudragi RL100, and almond gum spectra are shown in Figure 2.

The patches from the all formulation were all uniform, translucent appearance, and flexible with smooth surface. The diameter was 3.5 cm and the area was of 49 cm. The prepared batches of F_7 and F_8 are taken as best formulations after drying as shown in Figure 3. All the patches have uniform thickness throughout from formulations F_1 to F_4. The thickness of the various films varies from 0.17 ± 0.002 to 0.28 ± 0.041 mm with low standard deviation values. The thinnest being of F_1 and thickest of F_5 formulations are shown in Table 2.

The weight of 2 cm × 2 cm patch was in the range of 80-174 mg. It was observed that formulation F_1 and F_2 showed low average weight whereas formulation F_6-F_8 containing almond gum and HPMC showed high average weight as shown in Table 2.

The drug content in all formulations varies between 94.82 ± 0.02 and 99.83 ± 0.05. As the drug was uniformly dispersed in the matrix of the polymer, a significantly good amount of drug was loaded in the formulation. The order of drug content was found to be $F_7 > F_8 > F_5 > F_6 > F_2 > F_1 > F_4 > F_3$ as shown in Table 2. The acidic or alkali pH caused irritation to buccal mucosa and may affect the drug release and degree of hydration of polymers.Therefore, the surface

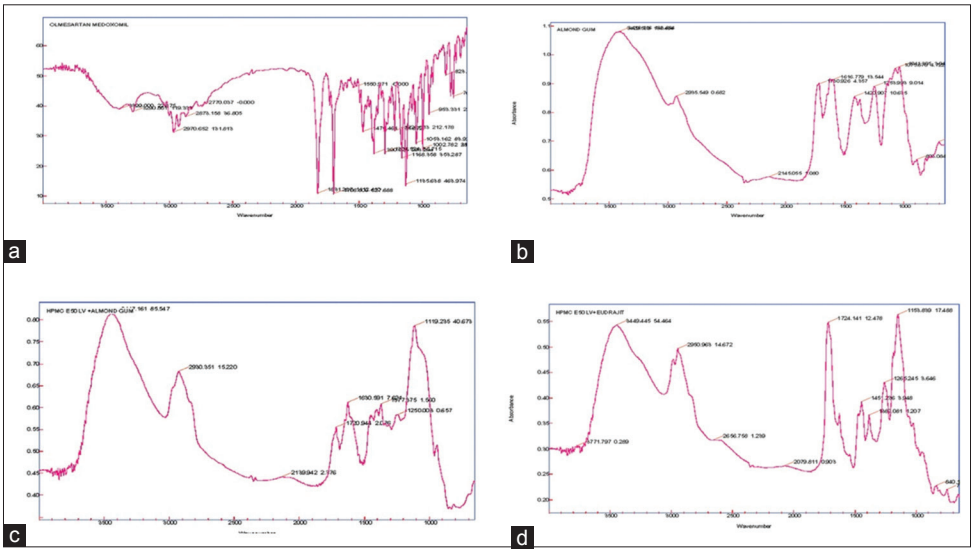

Figure 2: Fourier transform infrared (FTIR) studies: (a) FTIR of olmesartan medoxomil, (b) FTIR of almond gum, (c) FTIR of hydroxy propyl methyl cellulose (HPMC) E50LV and almond gum, (d) FTIR of HPMC E50LV and Eudrajit RL100

pH of buccal film was determined to optimize both drug release and mucoadhesion.The surface pH of all formulation is within ±0.5 units of the neutral pH, and hence no mucosal irritations were expected and ultimately achieve patient compliance as shown in Table 3.

The folding endurance was found to be in the range of 277 ± 0.0042-326 ± 0.062 and did not show any crack even after folding for more than 300 times. The values were found to be optimum to review good film properties. The comparative folding endurance in different formulation wherein the order of $F_1 > F_8 > F_5 > F_6 > F_4 > F_3 > F_2$ is shown in Table 3.

The swelling of films were observed at pH 6.8 phosphate buffer solution. The comparative percentage swelling behavior for various formulations is shown in Table. The percentage swelling of HPMC films was reduced by the addition of Eudarjit RL100 and increased by the addition of almond gum. The almond gum containing formulations F_5 showed higher percentage swelling due to freely soluble in water. The water soluble hydrophilic additive dissolves rapidly resulting in high porosity. The percentage moisture absorption and moisture loss was found to be minimal, hence ensures the stability of films in different environmental conditions. However, it was found that percentage moisture absorption and moisture loss is increased with increase in addition of hydrophilic polymers such as HPMC and almond gum (F_6-F_8). The percentage moisture loss and absorption in hydrophilic polymers were found to be high in F_5 when compared to F_1 as shown in Table 3.

Figure 3: Best formulations of F_7 and F_8

In vitro dissolution studies

The data obtained as shown in Table 4 for *in vitro* drug release study performed up to 7 h provide a clear indication that prepared patches show necessary controlled release profile desired for buccal adhesive drug delivery. The *in vitro* release studies of various formulations were performed in 500 ml pH 6.8 phosphate buffer solution at 257 nm as shown in Figure 4.

Among them, formulation F_5 shows highest drug release at the end of 7 h. It was observed that *in vitro* drug release

Table 2: Physico chemical characteristics for formulation F_1-F_8

Formulation	Thickness (mm)±SD, *n*=3	Average weight (mg)±SD, *n*=3	Drug content (%)±SD, *n*=3
F_1	0.17±0.002	80±0.05	97.49±0.03
F_2	0.19±0.004	80±0.003	98.10±0.001
F_3	0.22±0.002	120±0.003	94.82±0.02
F_4	0.24±0.006	142±0.86	96.62±0.11
F_5	0.28±0.041	159±0.081	98.64±0.09
F_6	0.24±0.009	162±0.024	98.26±0.02
F_7	0.23±0.026	168±0.002	99.83±0.05
F_8	0.26±0.040	174±0.004	99.24±0.06

SD: Standard deviation

Table 3: Physiochemical properties of buccal film

Formulation	Surface pH±SD, *n*=3	Folding endurance±SD, *n*=3	% SI±SD, *n*=3	% Moisture absorbance±SD, *n*=3	% Moisture loss±SD, *n*=3
F_1	6.39±0.025	326±0.062	56±2.642	10±0.14	1.52±0.026
F_2	6.35±0.096	277±0.0042	42±3.005	9.8±0.002	1.42±0.624
F_3	6.70±0.075	282±0.324	56±1.527	11.2±0.015	1.36±0.157
F_4	6.23±0.120	289±0.420	58±0.845	9.62±0.026	1.30±0.124
F_5	6.48±0.051	302±0.360	92±0.721	12.11±0.12	2.36±0.006
F_6	6.36±0.105	294±0.020	64±0.423	10.25±0.011	1.62±0.72
F_7	6.38±0.120	286±2.42	78±0.627	10.45±0.62	1.98±0.012
F_8	6.35±0.052	310±2.645	82±0.246	11.25±0.012	2.21±0.07

SD: Standard deviation

Table 4: *In vitro* dissolution studies of buccal films

Time in hrs	F_1	F_2	F_3	F_4	F_5	F_6	F_7	F_8
1	14.20±0.014	15.13±0.013	18.32±0.015	18.33±0.010	20.24±0.011	18.52±0.010	11.62±0.065	11.52±0.061
2	23.82±0.019	26.72±0.019	32.45±0.050	18.62±0.015	36.20±0.013	32.67±0.015	18.52±0.075	22.53±0.070
3	37.21±0.021	34.16±0.014	44.56±0.011	29.54±0.020	49.24±0.019	36.39±0.020	28.36±0.011	31.66±0.080
4	42.76±0.019	42.23±0.020	65.61±0.044	42.23±0.017	57.18±0.020	49.53±0.022	30.59±0.012	46.53±0.090
5	59.20±0.015	55.47±0.031	70.52±0.052	56.32±0.018	68.24±0.025	58.39±0.018	34.62±0.015	51.37±0.080
6	61.89±0.012	68.34±0.015	79.61±0.071	64.51±0.019	76.14±0.060	66.42±0.015	36.71±0.017	59.69±0.011
7	83.27±0.011	82.56±0.032	80.45±0.014	72.51±0.011	89.73±0.051	78.13±0.011	47.69±0.019	64.13±0.015

Table 5: Release kinetics study of optimized formulation (F_7)

Formulation code	Zero order	First order	Higuchi	Hixon Crowell	Korsemeyer–Peppas
FC_7	0.984393003	0.993780067	0.965535969	0.968806791	0.989525574

for formulation F_2-F_4 after 7 h was found to be in the order $F_2 > F_3 > F_4$ and was found that F_5 containing almond gum showed highest SI with release of drug when compared to F_1 containing HPMC alone. The formulation F_7 containing 2.5:1.5 of HPMC E50LV and almond gum showed highest SI which could retard the release of drug up to 18 h showing 47.69 ± 0.019 at the end of 7 h. The formulation F6 and F8 containing 3:1, 2:2 of HPMC E50LV and almond gum showed SI 64 ± 0.42 and 82 ± 0.246 with drug release of 78.13% and 64.13%. The rank order of drug release after 7 h was found to be 89.73% > 33.27% > 82.56% > 80.45% > 78.13% > 72.15% > 64.13% > 47.69% for formulation F_5, F_1, F_2, F_3, F_6, F_4, F_8, F_7, respectively, as shown in Figures 5 and 6. It was observed that during dissolution films containing equal amount of HPMC and almond gum swelled forming a gel layer on the exposed film surfaces. The loosely bound polymers molecules in these films were readily eroded, allowing the easy release of drug as compared to F_7. It was concluded that the formulation F_7 containing 2.5:1.5 of HPMC and almond gum showed good swelling a convenient residence time as well as promising drug release on the basis of release pattern and SI F_7 formulation chosen as the best formulation. F_7 proved to be a better candidate to other formulation of slow release for longer duration.

Release kinetics

Different model dependent approaches (zero order, first order, Higuchi, Korse Meyer-Peppas model was performed for best formulation F_7. The results of these models follow Korse Meyer-Peppas model as "best fit model" follows diffusion mechanism. This is due to previously proved fact depending on R^2 value obtained from model fitting. From the results, F_7 showed more retarding effect and thus found that $T_{50\%}$ value increases as concentration of almond gum increases. Korse Meyer-Peppas release exponent (n) values of all OMX l buccal film are >1 indicating drug diffusion is rapid due to swelling in the polymer as shown in Table 5 and Figure 7a-e.

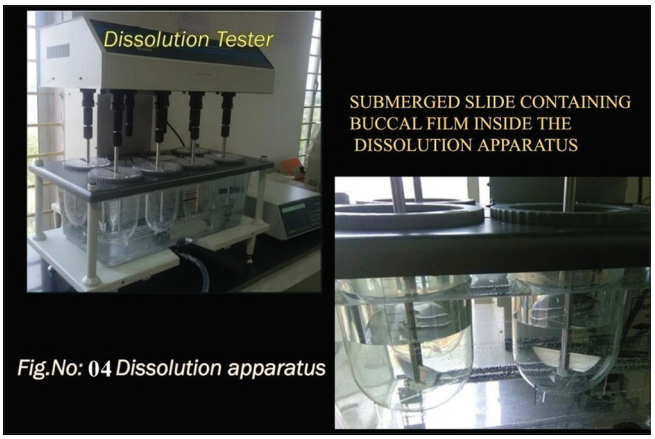

Figure 4: Dissolution apparatus and submerged slide containing buccal film inside dissolution apparatus

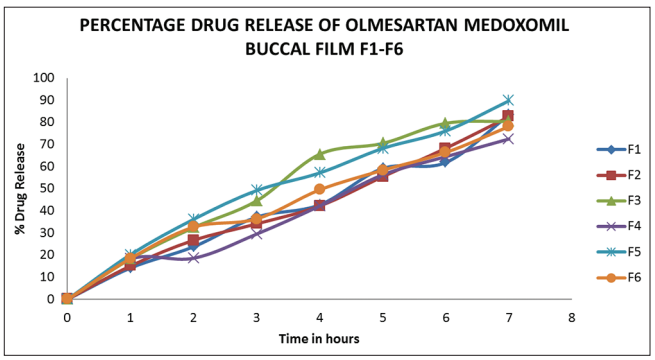

Figure 5: Percentage drug release of olmesartan medoxomil buccal films

Stability studies

According to ICH guidelines, stability study at room temperature for 7 days at RH 75 ± 5% of best formulation (F_7 and F_8) was carried out. It showed negligible change over time for parameters such as average weight, SI, folding endurance, percentage moisture loss, percentage moisture absorption, and *in vitro* drug release. There was no

significant difference in the drug content between initial and formulations stored at room temperature for 7 days at RH 75 ± 5% in a desiccator as shown in Table 6.

Table 6: Stability studies of best formulations (F_7 and F_8)

Parameters	After 7 days	
	F_7	F_8
Average weight (mg)	168±0.002	174±0.004
SI (%)	78±0.624	82±0.246
Percentage moisture loss	1.98±0.012	2.21±0.07
Percentage moisture absorption	10.45±0.62	11.25±0.012
In vitro release (%)	47.69±0.019	64.13±0.015
Folding endurance	286±2.42	310±2.645

SI: Swelling index

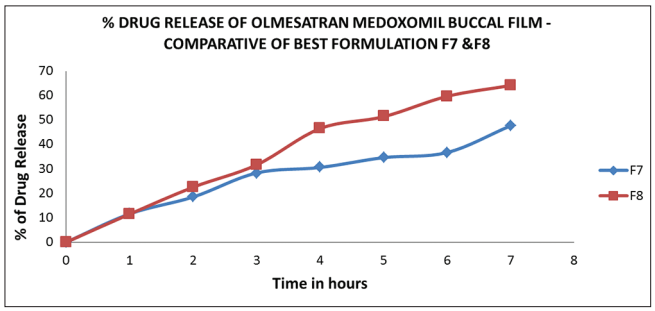

Figure 6: Percentage drug release of olmesartan medoxomil - comparative of best formulations

CONCLUSION

The results of all the physical characterization of all formulation F_1-F_8 were found to be satisfactory. The results of the study show that therapeutic levels of OMX can be delivered through buccal. The present study concludes that these erodible mucoadhesive buccal films containing olmesartan can be very promising for effective doses to systemic circulation. These may also provide an added advantage of circumventing the hepatic first pass metabolism. The films exhibited controlled release over more than 7 h. It was concluded that the films containing 14 mg of OMX in HPMC E50LV and almond gum (formulation F_7) showed good swelling and promising controlled drug release. Thus, F_7 buccal film can be used for effective therapeutic uses. Buccal films have gained relevance in pharmaceutical industry as a novel, patient-friendly convenient products. The study may be extended for assessing the *in vivo* release and *in vitro–in vivo* correlation. The future scope could be tested in human volunteers to evaluate bioavailability parameters.

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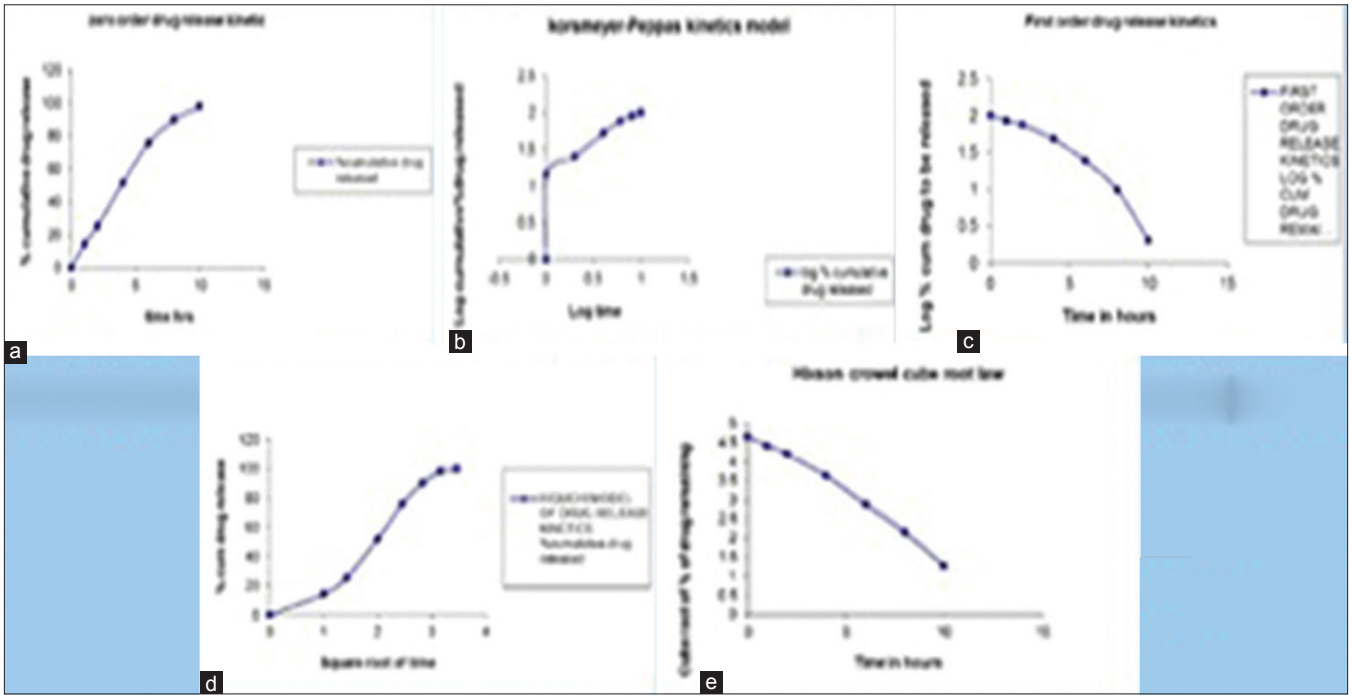

Figure 7: Release kinetics studies: (a) Zero order kinetics, (b) first order kinetics, (c) Korsmeyer–Peppas model, (d) Higuchi model, (e) Hixson Crowell model

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