AMERICAN JOURNAL OF PHARMTECH RESEARCH

Journal home page: http://www.ajptr.com/

Design and Evaluation of Buccal Films of an Antihypertensive Drug

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ABSTRACT

Olmesartan medoxomil is an angiotensin II antagonist used as an antihypertensive drug which has poor oral bioavailability. Hence, an attempt was made to prepare and evaluate mucoadhesive buccal films containing Olmesartan medoxomil as model drug. Various mucoadhesive buccal films were prepared by employing HPMC alone, and in combination with Eudragit RL100, Carbapol 934, Ethyl cellulose were prepared by solvent casting method using ethanol , water and acetone as solvents, tween 80 as solubilising agent and glycerine as plasticizer. The prepared mucoadhesive buccal films were evaluated for their physic-chemical parameters such as thickness uniformity, weight uniformity, folding endurance, drug content , surface pH, swelling index, bioadhesion, percentage moisture loss and uptake, vapor transmission rate. The formulations exhibited good results. *In – vitro* drug release studies were conducted for OLM loaded films in phosphate buffer (pH 6.8) solution. The drug release was in the range of 67 to 90 % in 6hrs.. Stability studies were carried out with selected formulation. *In- vivo* release was evaluated in rabbits by patch test and it showed good correlation with *the in-vitro* release data. Drug release was found to be diffusion following zero order as per kinetic studies.

Keywords: Mucoadhesive buccal films,Omedoxomil, HPMC, Carbopol 934, Eudragit, Ethyl cellulose, swelling study, Bioadhesion, *in – vitro* release, *in-vivo* study.

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Received 13 August 2012, Accepted 28 August 2012

Please cite this article in press as: Pednekar T *et al.*, Design and Evaluation of Buccal Films of an Antihypertensive Drug. American Journal of PharmTech Research 2012.

INTRODUCTION

Buccal drug delivery has lately become important route of administration. The rich vascularisation of the oral mucosa and its permeability to many drugs makes this route an attractive alternative to oral or parenteral route for systemic drug delivery[4].

Thus oral mucosa route of drug delivery has attracted the attention worldwide for optimizing the drug delivery. Muco-adhesive buccal films may be preferred over adhesive tablets in terms of flexibility and comfort and also they do not get easily washed away or removed by saliva as may in case of oral gels[1,2,3]

Many antihypertensive drugs are used in the treatment of congestive heart failure, cardiac arrhythmias and angina pectoris. It exhibits poor bioavailability of 25-30% which is attributed to its poor solubility and metabolic degradation. The present work is aimed at overcoming these limitations of Olmesartan medoxomil which exhibits poor bioavailability of 26% so that it does not remained confined to combination therapy. It has a starting oral dose of 20mg which can be increased upto 40 mg beyond which it does not show any much advantage. it has an elimination half life of 10-12hrs.owing to its high protein binding the drug has dose related side effects Also the dose can be reduced owing to the increased bioavailability[6,7,8]

MATERIALS AND METHODS

Olmesartan medoxomil was obtained as a gift sample from Astrazeneca, Bangalore, India.HPMC 50 cps, Eudragit was obtained from Yarrow chem.. Products, Mumbai whereas Carbapol 934 and Ethyl cellulose was procured from Manipaal drugs, Karnataka.

Preformulation studies[3]

The polymer and drug compatibility was checked by FTIR analysis (Jasco FTIR4100) by using potassium bromide discs to ensure there was no incompatibility. λmax determination of Olmesartan medoxomil was done by UV spectroscopy using phosphate buffer pH6.8 and a calibration curve of Olmesartan medoxomil was plotted by taking 2-18 µg/ml which was measured at 257nm using phosphate buffer solution pH6.8 as blank[9].

Preparation of films

The films containing Olmesartan medoxomil were prepared by solvent casting technique using film forming polymer HPMC alone and in combination with Eudragit, Carbapol934, Ethyl cellulose using solvents such as ethanol (drug, HPMC, Ethyl cellulose), acetone (Eudragit), water (carbapol). Tween 80 was used as solubilising agent and glycerine was used as plasticizer. Drug-polymer solution was prepared by stirring on magnetic stirrer and then films were casted in

glass mould (5x2 $cm^{2)}$. 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 hrs-72 hrs, then were packed in aluminium foil and stored in dessicator.

Table 1: Formulation chart for F1 to F6

Ingredients	F_1	F_2	F_3	F_4	F_5	F_6
Olmesartan medoxomil,mg	50	50	50	50	50	50
HPMC,mg 50cps	250	150	200	200	150	200
Eudragit RL100,mg	-	100	50	-	-	-
Carbapol 934,mg	-	-	-	50	100	-
Ethyl cellulose,mg	-	-	-	-	-	50
Glycerine (1 drop)	0.0588	0.0588	0.0588	0.0588	0.0588	0.0588
Ethanol, ml	10	8	8	7	7	10
Acetone, ml	-	2	2	-	-	-
Tween 80, ml	0.1	0.1	0.1	0.1	0.1	0.1
Water, ml	-	-	-	3	3	-

EVALUATION OF FILMS

Appearance and texture

The films are observed visually for their physical appearance such as colour and transparency The films were examined for their surface texture such as smooth, rough or very smooth[1,27.]

Film thickness

Assessment of thickness is done on 5 films using micrometer screw gauge and the standard deviation is also calculated.[11, 26]

Folding endurance:

The folding endurance of the films is determined by repeatedly folding one film at the same place up to maximum 300 times or till it broke. [10, 12]

Swelling index:

The films are cut into 1 x 1cm were weighed accurately and kept immersed in 50 ml water. The films were taken out carefully at 5, 10, 30 and 60 mins interval blotted with filter paper to remove the water present on their surface and weighed accurately, the swelling index is calculated using formula[12]

Swelling index (S.I) = initial wt-final wt/ initial wt×100

Bioadhesion strength:

The apparatus consisted of a modified double beam physical balance in which a lighter pan had replaced the right pan and the left pan had been replaced by glass slide (4cm length and 2.5 cm width) with plastic hang. Both sides of the balance were made equal by adding 5gm weight to

the right hand pan. The height of total setup was adjusted to accommodate a glass container. The balance is kept in this position for 5 min contact time. And the weight required to detach the patch from the vial is determined[13].

Tensile strength[13, 25]

This is done by a Universal strength testing machine with two plates made up of Plexiglas's. One plate is in front and is movable part of device and can be pulled by loading weights on the string, which is connected to movable part. The 5 x1 cm^2 buccal formulation is fixed between the stationary and movable plate. The force needed to fracture the film is determined by measuring the total weight loaded in the string.

Uniformity of weight of the films[16, 24]

Films of 1x1 cm^2 are cut. The weights of 5 films were taken using digital balance and the weight is calculated.

Drug content uniformity of the films [14, 20]

A film size 1x1cm^2 is cut and place in a beaker. Add 100ml of phosphate buffer pH 6.8. The contents are stirred and mixed to dissolve the film. The contents are transferred to a volumetric flask. After suitable dilution, the absorbance of the solution was observed using UV-Visible spectroscopy against phosphate buffer pH 6.8 as blank at 257 nm.

Surface pH[23]

The films were tested for their surface pH by taking a patch in 25ml phosphate buffer pH 6.8 , dissolving it completely and then introduced to pH meter.

Percentage moisture absorption[15]

The percentage moisture absorption test was carried out to ensure physical stability or integrity of buccal films. Buccal films were weighed and placed in a desiccator containing 100 ml of saturated solution of aluminium chloride and 75 ± 5% RH was maintained. After three days the buccal films were taken out and reweighed. The percentage moisture absorption was calculated using this formula

%Moisture absorption= Final weight- Initial weight / Initial weight x 100

Percentage moisture loss[15]

The percentage moisture loss was carried out to evaluate integrity of the film in dry conditions. Buccal films were weighed and kept in a desiccator containing anhydrous calcium chloride. After three days, the patches were taken out and reweighed. The percentage moisture loss was calculated using the formula

$$\%\text{Moisture absorption} = \frac{\text{Initial weight- Final weight}}{\text{Initial weight}} \times 100$$

Vapour Transmission Rate (VTR) [16]

Vapour transmission method was employed for determination of vapour transmission from the patch. Glass bottle filled with 2g anhydrous calcium chloride and an adhesive (Feviquick) spread across its rim was used in the study. The patch was fixed over the adhesive and the assembly was placed in constant humidity chamber, prepared using saturated solution of ammonium chloride and maintained at 37±20C. The difference in weight after three days was calculated. The vapour transmission rate was obtained as follow:

$$\text{Vapour transmission rate (VTR)} = \frac{\text{(Amount of moisture transmitted)}}{\text{Area} \times \text{Time}}$$

Loss on drying[17]

The drying was carried out in an oven with a temperature above the temperature of solvent evaporation at atmospheric pressure. The LOD is the loss of mass expressed as percent (w/w). The weight of the films was measured until constant mass was achieved to ensure complete removal of residual solvent.

***In-vitro* release study**[18, 22]

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^{o} 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 6hrs. The sink condition was maintained throughout the study. The samples were analyzed at 257 nm in a UV-VIS Spectrometer and cumulative amount of drug release at various time intervals was calculated.

Kinetic release studies:

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

Stability studies [19]

Best formulation was stored in screw capped small glass bottles at room temperature and in stability chamber at 40±1ºC and 75 % relative humidity. Samples were analyzed for physical appearance, residual drug content and in vitro release after a period of 15, 30, 45 days. Initial drug content was taken as 100% for each formulation.

In-vivo drug release study in rabbit [21]

After the approval of institutional animal ethical committee the *in-vivo* absorption studies of olmesartan medoxomil buccal film was conducted on rabbits. Three male rabbits weighing 2.0 to 5.0 kg were used for the release study of the olmesartan medoxomil. The animals were fasted for overnight with adlibitum storing them in individual cages before the experiment was carried out. The rabbits were anesthetized with Phenobarbital sodium IP (1ml containing 200 mg) by intra peritoneal route. Films of size 1 x 1 cm^2 were cut and fixed on a cellophane paper which acted as a backing layer so that the drug release was made unidirectional and threads tied to it, so that the films were easily removed from the buccal cavity. After 30 min of the anesthetic injection, the films were placed (seperately) in the buccal cavity one at a time. After a gap of 2 min further films were attached. The films were taken out at 1, 2, 3, 4, 5, 6^{th} hours the process was repeated two more times to validate the result. The films were were diluted suitably with phosphate buffer pH 6.8.and the drug remained unabsorbed was analysed at 257 nm.

RESULTS & DISCUSSION

Preformulation studies on drug

Olmesartan medoxomil λ max was determined to be 257nm. The calibration curve with concentration 2- 18 µg/ml obeyed Beer's law.

All the characteristic IR peaks related to pure drug, Olmesartan medoxomil were also appear in the IR spectrum of mixture of drug with polymers, so there was no any chemical incompatibility between drug and polymers. Functional groups and their IR range of Olmesartan medoxomil, HPMC, Eudragit, Ethyl cellulose and Carbopol 934. spectra are shown in Figure 1,2,3,4,5.

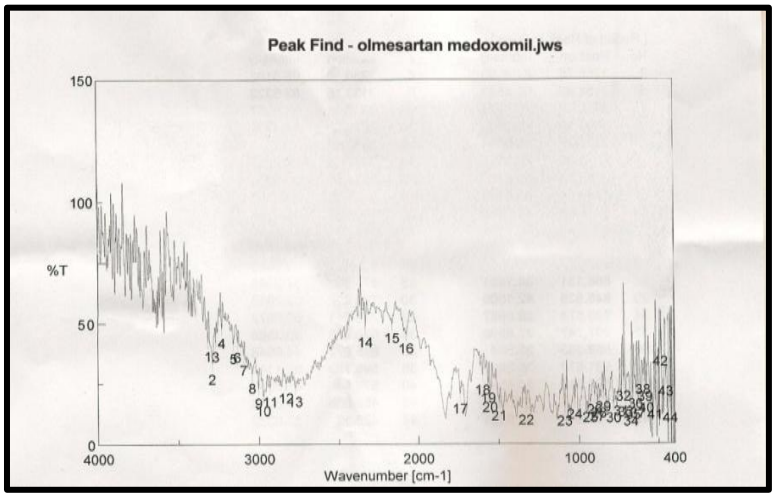

Figure 1. IR spectra of pure drug

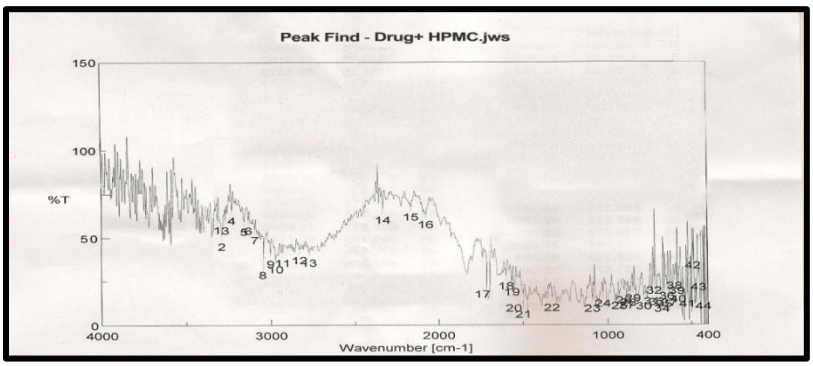

Figure 2. IR spectra of drug+ HPMC

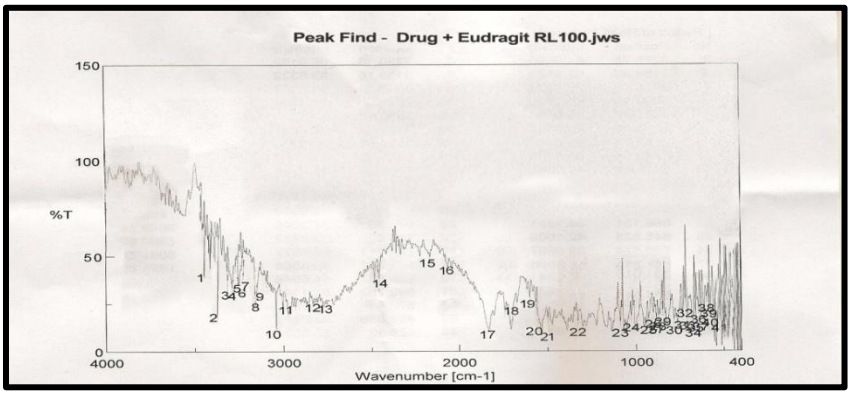

Figure 3. IR spectra of drug+ Eudragit

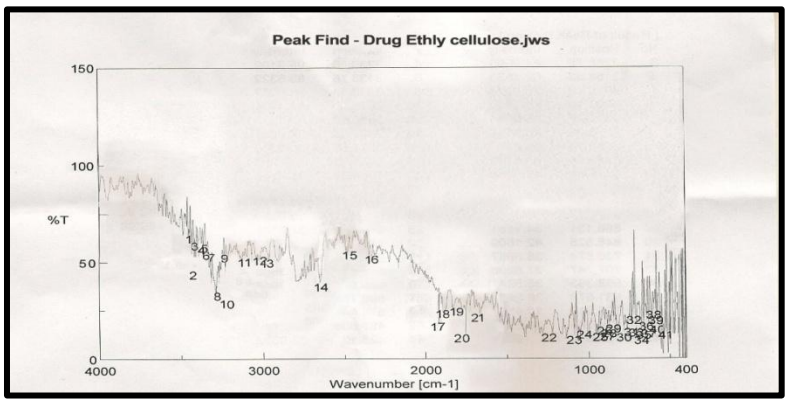

Figure 4. IR spectra of drug+ Ethylcellulose

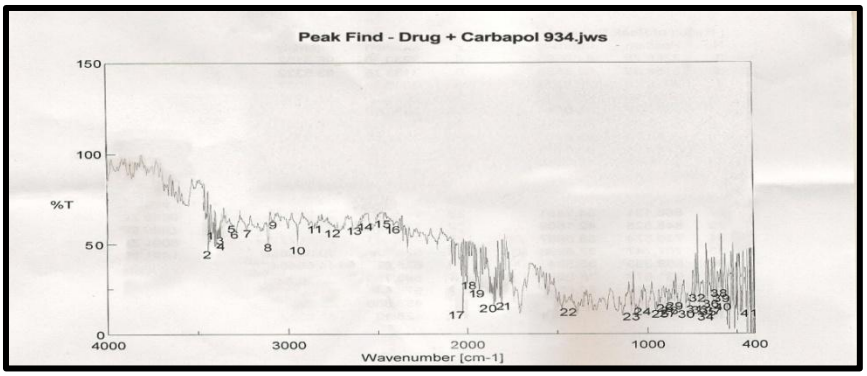

Figure 5. IR spectra of drug+ Carbapol 934

The appearances of the films prepared are all uniform having translucent appearance flexible with smooth surface texture. The thickness of the various films varies from 0.174 to 0.196 mm with low standard deviation values.

The folding endurance of the films was measured manually. The folding endurance for all the formulation was found to be more than 300 times which was satisfactory to reveal good film properties. Folding endurance was found to be between 326 to 382.

The results showed that the swelling index of HPMC films containing Carbopol (F4 andF5) were more than the other films .It was observed that there was a proportionate increase in concentration of polymer increases swelling index. However all films showed considerably good swelling behaviour ranging between 60.41% to 48.76% (Table 2)

Table 2: Physico-chemical properties for formulation F1 to F6

Formulation	Thickness (mm)	Weight variation (mg)	Folding endurance	Tensile strength (kg/cm^2)	Bioadhesive strength (gms)	Swelling index (%)
F1	0.196 ± 0.002	37.42 ±0.012	334 ± 5	1.02 ± 0.002	13.66 ± 0.02	56.07± 0.01
F2	0.178 ±0.001	38.44 ± 0.036	332 ± 5	1.25 ± 0.021	12.16 ± 0.001	51.41± 0.001
F3	0.182 ± 0.001	38.14 ± 0.036	330 ± 3	1.2 ± 0.004	11.77 ± 0.021	52.38± 0.004
F4	0.186 ± 0.002	44.44 ± 0.016	338 ± 2	1.11 ± 0.02	12.75 ± 0.02	60.36± 0.007
F5	0.198 ± 0.001	45.46 ± 0.036	341 ± 5	1.13 ± 0.002	14.56 ± 0.024	56.61± 0.011
F6	0.174 ± 0.002	37.1 ± 0.021	328 ± 4	1.24 ± 0.001	9.66 ± 0.002	48.76± 0.003

In the next phase bioadhesive strength was determined for the all the formulations using fabricated equipment. The results indicated that the bioadhesive strength was found to have some variation because combination of two hydrophilic polymers would result in better bioadhesion than combination of hydrophilic and hydrophobic polymers. However all the films showed good bioadhesion. The readings obtained were between 11.16 gms to 14.56 gms with low SD values .

Then tensile strength was observed. it was seen that HPMC alone had less tensile strength when compared to combination. It ranged between 1.02 ± 0.002 to 1.25 ± 0.021. An increase in tensile strength was observed with increase in polymer concentration however formulation F2 and F6 containing HPMC with Eudragit and Ethyl cellulose had maximum tensile strength(Table 2).

The average weight of formulation was found to be between 37.1 ± 0.021 to 45.46 ± 0.036. In which Eudragit RL-100 was used as copolymer there was no much weight variation observed.

But a considerable weight variation was observed in case of F5, F6 formulations in which Ethyl cellulose and Carbopol were used as compared to other formulations. The pH of the films was estimated and it found to be between 6.7 to 6.9 with low SD value (Table 2).

Later, the drug content was estimated in all the formulation using standard method. The drug content of all the films was found to be within permissible range with low SD values, which indicates that the drug distribution was uniform in all the films. It varied from 97.15 ±0.081 to 100.37 ± 0.05 (Table 3).

Table 3: Physico-chemical properties of films (drug content, PMA, PML, VTR)

Formulation	Drug content (%)	% moisture absorption	% moisture loss	Vapour transmission rate(g/cm^2/hr)
F1	100.37 ± 0.05	4.98 ± 0.014	2.95 ± 0.012	2.37 ± 0.005
F2	99.62 ± 0.003	2.25 ± 0.002	1.51 ± 0.024	1.62 ± 0.013
F3	98.75 ± 0.083	2.61 ± 0.01	1.8 ± 0.003	1.75 ± 0.08
F4	98.26 ± 0.081	5.21 ± 0.004	2.16 ± 0.004	3.26 ± 0.081
F5	97.15 ±0.081	5.01 ±0.015	1.78 ±0.011	3.15 ±0.07
F6	98.88 ± 0.012	3.48 ± 0.022	1.98 ± 0.007	2.18 ± 0.012

The percentage moisture absorption (% PMA) and percentage moisture loss (% PML) was found to be minimal hence ensures the stability of films in different environmental conditions. However it was found that the % moisture absorption and loss increased with increase in hydrophilic polymers like HPMC and Carbapol (F1, F4, F5) (Table 3).

All formulation showed optimum values of VTR. However the combination of hydrophobic and hydrophilic polymers produced a resistance for vapour transmission. It ranged between 1.62 to 3.26 g/cm sq/hr with low SD (Table 3).

After evaluation of all the films for their physic-chemical parameters, they were subjected to in – vitro drug release studies carried out using 500 ml phosphate buffer of pH 6.8 in USP type II apparatus. The release data of olmesartan medoxomil from all the films are given in (Table 4, 5).

Table 4: Results of *in-vitro* drug release (F1 to F6)

Time	F1	F2	F3	F4	F5	F6
0	0	0	0	0	0	0
60	15.58±0.014	10.02±0.013	12.06±0.011	14.28±0.017	14.65±0.03	12.43±0.022
120	28.79±0.002	23.21±0.002	25.44±0.03	28.04±0.074	29.34±0.007	26.37±0.037
180	45.51±0.011	33.63±0.019	37.34±0.013	40.87±0.0081	42.36±0.052	39.76±0.015
240	58.16±0.003	47.56±0.002	46.64±0.009	54.07±0.081	56.67±0.018	49.99±0.007
300	75.26±0.021	55.57±0.007	62.62±0.011	71.17±0.056	73.40±0.174	64.30±0.001
360	90.88±0.004	68.16±0.003	72.12±0.007	85.3±0.019	88.28±0.052	78.24±0.017

In case of formulation F1 to F6 the release data of Olmesartan medoxomil from all the films indicated that the drug release was higher i.e 90.88% in HPMC (F1) alone. Eudragit retarded the release rate of drug from HPMC films (F2 and F3). An increase in the polymer content was

associated with a corresponding decrease in the drug-release rate F2 shows in-vitro drug release 68.75 in 6 hours. It proved to be a better candidate compared to other formulation for slow release for longer duration (Table 4).

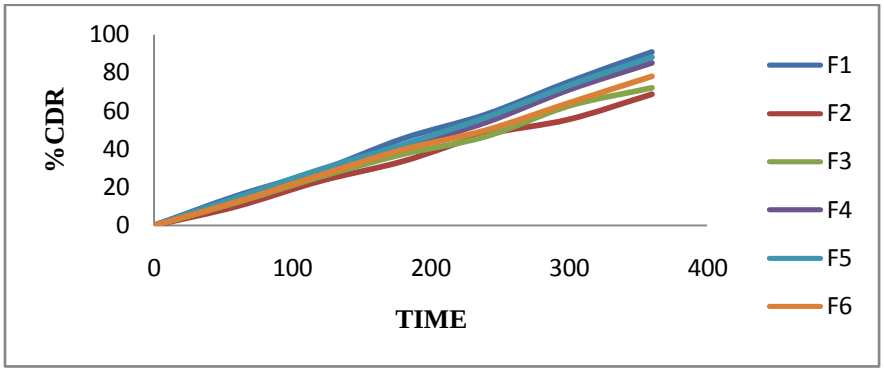

Figure. 6: *In-vitro* drug release profile (F1 to F6)

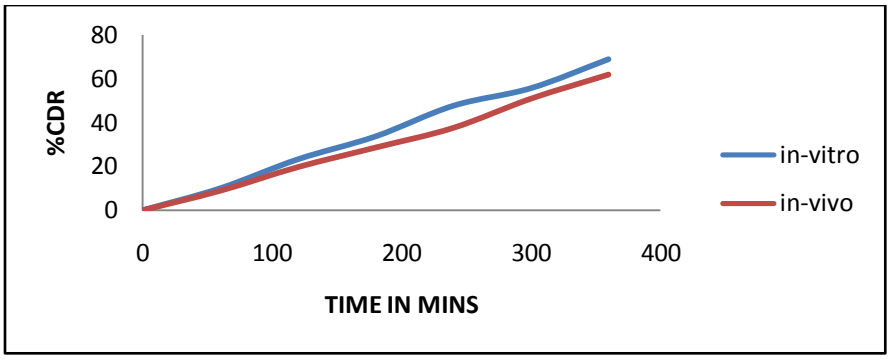

Figure. 7: In-*vitro, in-vivo* release profile

Kinetic model fitting was carried out for formulation F1 to F6 to understand the order and mechanism of drug release the high regression value between (0.9991 to 0.9978) suggested the rate of drug release followed zero order kinetics. The data was fitted with Higuchi equation which yielded almost liner plots with their high regression co-efficient between (0.9907 to 0.9764) indicating the mechanism was non-fickian diffusion with their 'n' values between (0.7102 to 0.7548).

Stability studies were then carried out using F2 formulation (HPMC and Eudragit) for a period of 45 days at room temperature and in stability chamber at 40±1ºC and 75 % relative humidity. It was found that the films retained its appearance and there was no much fluctuation in the values of drug content and in-vitro release data. Hence the formulation was found to be stable on storage.

In-vivo studies were carried out using rabbit's .It was seen that there was a slower release of drug from films than the *in-vitro* release. The release after 6hrs was found to be 63.7% (Table 5) it was then subjected to different kinetic models and the release was determined to be diffusion

following zero order kinetics. It was also confirmed by korsmeyer's equation that the diffusion was non-fickian owing to n value being above 0.5 (0.69).

Table 5: Results of *in-vivo* drug release (F2)

Time in mins	F2 % drug release
60	8.88±0.018
120	19.62±0.009
180	28.51±0.008
240	41.48±0.015
300	50.74±0.007
360	63.7±0.037

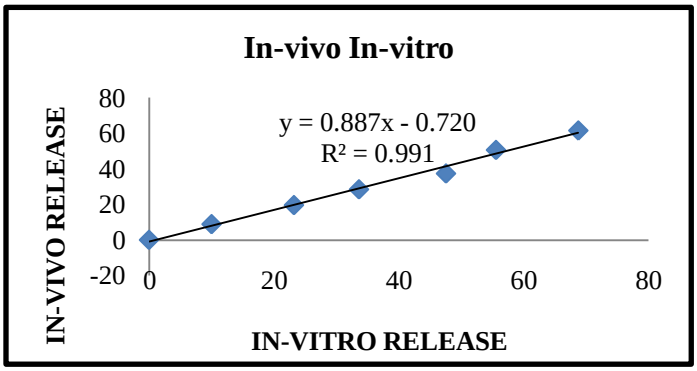

Figure 8: *In-vitro in-vivo* regression plot

In vitro release studies and their correlation with *in vivo* studies will be helpful to predict therapeutic efficiency of the dosage form. So to determine correlation the data of *in vitro* release and *in vivo* release of OLM from patch F2 was regressed using MS-Excel statistical program to understand *in vitro* and *in vivo* correlation. A good correlation observed (R2 = 0.9917) for the film F2.

CONCLUSION

It was thus concluded that Olmesartan medoxomil films could be prepared for slow release of drug using the different rate controlling polymers to treat hypertension. The films had good physico-chemical properties and HPMC with Eudragit could retard the release of drug. The FTIR studies proved that there were no signs of interactions. Selected formulation F2 was found to be stable. Also the *in-vivo* release showed good correlation with *in-vitro* drug release. The future scope could be testing in human volunteers to evaluate bioavailability parameters.

ACKNOWLEDGEMENT

The authors are thankful to Astrazeneca, Bangalore to supply gift sample of Olmesartan medoxomil and also thankful to Srinivas College of Pharmacy for providing necessary facilities for completion of work.

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