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RESEARCH ARTICLE

Formulation and Evaluation of Fast Dissolving Buccal Patch of Olmesartan Medoxomil

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ABSTRACT

Now days tablet dosage forms are supplanted by new drug delivery system because of problems like hepatic metabolism, GI toxicity and enzymatic degradation which leads to non-compliance and ineffective therapy. These problems can be overcome by formulating the drug into fast dissolving buccal patches for oromucosal absorption with fast onset of action and improved bioavailability. In present work the fast dissolving buccal patches of Olmesartan medoxomil was prepared by solvent casting method using HPMC E5, HPMC 3cps and HPMC K100 as a film formers and PEG 400 as plasticizer. The prepared patches were evaluated for weight, thickness, folding endurance, surface pH, disintegration time, *in-vitro* drug release and stability studies on optimized formulation. The thickness of the all patches was found in the range of 0.22 to 0.30 mm. The disintegration time was found up to 60 sec. and the folding endurance was up to 200. The *in-vitro* drug release was found to be up to 100% within 2 minutes. Thus the fast dissolving buccal patch of Olmesartan medoxomil was successfully formulated to achieve a safe, rapid and effective dosage form with enhanced drug dissolution and rapid antihypertensive therapy.

Keywords: Fast dissolving buccal patch, HPMC, Solvent casting method, *in-vitro* drug release.

1. INTRODUCTION:

Buccal drug delivery system is an alternative to other conventional methods of systemic drug administration as buccal mucosa is relatively permeable with rich blood supply and acts as a better site for the drug absorption. The buccal route of drug administration provides direct entry into the systemic circulation by avoiding the hepatic metabolism of the drug molecule and enzymatic degradation of the drug in the gastrointestinal environment. This route of drug administration also offers self medication with low dose as possible. Hence it is accepted as safe and effective route of drug administration. The various buccal dosage forms include fast dissolving buccal patches, tablets, oral wafers, chewing gums and jellies. Among these dosage forms the fast dissolving buccal patches show great advantages over other dosage forms like ease of administration, patient compliance, facility to incorporate permeation enhancers in the formulation and dose delivery can be terminated in case of emergency makes it more preferable dosage form. The buccal patch is mainly composed of active pharmaceutical ingredient, film forming polymers and plasticizers. The plasticizers provide strength and rigidity to the film. After application of the patch it adheres to the mucosa of the buccal cavity due to hydration of the patch by saliva. Saliva is responsible for the hydration and finally disintegration of the dosage form in the mouth. This dosage forms has certain advantages that make it well accepted over other. In this dosage form no water is required for swallowing the medicaments also low doses can be administered by formulating into buccal patches. The bioadhesive polymers used in the formulation show some mucoadhesive property which increases the retention time of the dosage form at the site of application resulted in more and faster absorption of the drug through oromucosal tissues by avoiding first pass metabolism of the drug. While in adverse effect conditions drug action can be terminated by removing the dosage

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form from the site of application. (Mujoria R., et. al., 2011, Arya A., et. al., 2010 and Parmar H., et. al., 2010)

Olmesartan medoxomil (OLM) is chemically 2,3-dihydroxy-2-butenyl 4-[1-hydroxy-1-methylethy]-2-propyl-1-[p(o-1H-tetrazol-5-ylphenyl) benzyl] imida-zole-5-carboxylate, cyclic 2,3-carbonate, angiotensin II receptor antagonist used in the treatment of hypertension. The main drawbacks of conventional OLM formulations are hepatic metabolism and enzymatic degradation in the gastrointestinal tract which leads to decreased bioavailability. (Yadav A. A., et. al., 2012 and Drug Bank Database)

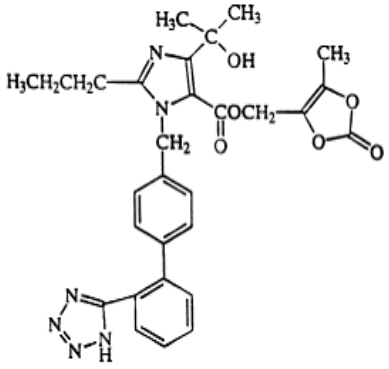

Figure 1: Chemical structure of Olmesartan medoxomil

The present work aimed to formulate the fast dissolving buccal patches of OLM to bypass the hepatic metabolism of the drug and to provide quick onset of action by oromucosal absorption of drug into the systemic circulation and also to reduce the dose size with minimal adverse effects results in better patient compliance with more effective hypertension therapy.

2. MATERIALS AND METHODS:

2.1. Materials:

The pure drug sample of Olmesartan medoxomil was supplied by Macleod Pharma Mumbai. HPMC (E5 and K100) and PEG 400 was obtained as gift samples from Vergo Pharma Research Goa. HPMC 3cps was gifted by BASF India Ltd. Mumbai. All other chemicals used were of analytical grade.

2.2. Methods:

2.2.1. Preparation of buccal patch:

The fast dissolving buccal patch was prepared by dissolving the film forming polymers (HPMC) in the water followed by addition of PEG 400 as plasticizer to the resulted polymer solution. The above solution was allowed to stir on the magnetic stirrer for 4 h to homogenize the solution. Then the solution kept in the vacuum desiccators to remove the air bubbles. Meanwhile, in the separate beaker the solution of all water soluble ingredients with OLM is prepared and allowed standing for 45 minutes. Finally both the solutions was mixed and homogenized on the magnetic stirrer for another 1 h. Then the solution was casted into the Petri plates for drying into the oven at 50^0C for 24 h. After drying the film was cut into suitable size and stored in aluminium foil in well closed container. (Kaur M., et. al., 2013 and Kulkarni S., et. al., 2010)

Ingredients*	F1	F2	F3	F4	F5	F6
OLM	20	20	20	20	20	20
HPMC E5	-	500	-	200	300	300
HPMC 3cps	500	-	-	200	200	-
HPMC K100	-	-	500	100	-	200
PEG 400	4	4	4	4	4	4
Crospovidone	5	5	5	5	5	5
Water	q. s.	q. s	q. s.	q. s.	q .s.	q. s.
Ethanol	q. s.	q. s.	q. s.	q. s.	q. s.	q. s.

* All quantities are expressed in mg except PEG 400, Water and Ethanol in ml

Table 1: Composition of fast dissolving buccal patch of OLM

2.2.2. Evaluation of fast dissolving buccal patch: (

Jose J., et. al., 2012, Kulkarni S., et. al., 2010, Arya A., et. al., 2010 and Baviskar D., et. al., 2009)

Weight of patch:

The uniformity of weight for prepared buccal patches was analyzed by weighing the patches on the electronic balance (Shimadzu Corporation).

Folding endurance:

A patch of 1x1 cm size was cut evenly and folded repeatedly at the same place till it brakes. The number of times of folding at the same place without breaking gives the value for folding endurance.

Thickness:

The thickness of the all prepared patches was measured by using digital vernier caliper (Digimatic Digital Vernier Caliper, Mitutoyo, Made In Japan). The measurement was done at three different corners.

Surface pH:

The surface pH was measured by using digital pH meter. Initially the buccal patches were wet by 0.5 ml of water and allow equilibrating for 10 min. Then glass electrode of pH meter was placed in contact with the surface of the wetted patch. It reports the surface pH of the patch on the pH meter.

Disintegration time:

The time required to disintegrate was measured by disintegration time. The patch was placed in the disintegration test apparatus (Indo Sathi Scientific Lab) containing phosphate buffer having pH 6.8. Instrument was operated until patch gets disintegrate. The time required for disintegration was noted.

Drug content uniformity:

The prepared patch was dissolved in the 0.1N HCL and then absorbance was taken at 257nm. Concentration of

drug in the formulation was calculated using standard calibration curve of OLM.

Swelling index:

The patch was weighed and placed on a pre-weighed cover slip. The cover slip was then submerged in a petridish containing 20 ml phosphate buffer (pH 6.8). Increase in weight of the film was determined at regular time intervals until a constant weight was obtained. The hydration ratio of the patch was calculated using following formula. Where, W_t was weight of film at time t and W_0 was weight of film at zero time.

$$Swelling\ index\ (\%) = Wt - W0/W0 \times 100$$

2.2.3. Morphology study by Scanning Electron Microscopy:

Scanning electron microscope (JEOL-JSM- 6360, Japan) was used to study the morphology of the patch. The samples were attached to the slab surfaces with single-sided adhesive tapes and the scanning electron photomicrograph was taken at 100 X magnification at an acceleration voltage 10kV.

2.2.4. *In-vitro* drug release study:

The dissolution studies were carried out by using USP Type II dissolution test apparatus (Veego VDA-8DR) in 300 ml of phosphate buffer having pH 6.8 at 37±0.5^{0}C and at 50 rpm. The patch was submerged into dissolution media and aliquot of 5ml was withdrawn at 0, 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4 and 5 minute time intervals. An equal volume of dissolution medium was added to the chamber after every withdrawal of aliquot to maintain the sink condition. The collected samples were filtered through the whatmann filter paper and analyzed spectrophotometrically at 257nm using UV-Visible Spectrophotometer (Shimadzu-1800, Japan).

2.2.5. Stability studies:

The optimized buccal patch formulation was placed in the stability chamber (Remi Motors Ltd., Mumbai) at 40^{0}C temperature and 75% relative humidity for 3 months. After stability testing the patches again evaluated for drug content, Surface pH, folding endurance and *in-vitro* drug release. (Lalatendu P., et. al., 2004 and Dharani S., et. al., 2010)

3. RESULT AND DISCUSSION:

3.1. Evaluation of fast dissolving buccal patch:

Determination of weight, thickness, visual appearance, disintegration time and drug content values for the OLM patch are shown in Table 2. Disintegration time was found in the range 20 seconds to 60 seconds. Very less disintegration time resulted in faster dissolution of drug. Weight of all formulations was in the range of 30 to 36 mg. Folding endurance was found to be between 172-200.

3.2. Swelling index:

The swelling index of all formulations is given in Table 2. The formulation F2 showed high swelling index than other formulations. As the value of swelling index increases, the disintegration time of the formulation decreases. (Jangjid M., et. al., 2010)

Formulation	Weight (mg)	Thickness (mm)	DT (sec)	Folding endurance	Drug content (%)	Surface pH	SI (%)
F1	32	0.22±0.072	40±0.49	190±1.13	97.04±0.89	6.1±0.44	0.45±0.07
F2	34.5	0.24±0.052	20±0.69	200±1.35	99.17±0.79	6.9±0.57	0.84±0.06
F3	33	0.25±0.067	48±0.56	188±1.37	90.89±1.18	6.7±0.55	0.44±0.07
F4	30	0.22±0.091	60±0.63	172±1.08	94.45±0.74	6.5±0.72	0.60±0.06
F5	36	0.27±0.067	35±0.93	197±1.61	92.99±1.31	6.6±0.69	0.53±0.05
F6	33	0.24±0.073	40±0.58	181±1.55	96.33±0.94	6.8±0.60	0.55±0.06

DT: Disintegration time, SI: Swelling index, All values are expressed as mean ± S.D. (n=3)

Table 2: Evaluation of fast dissolving buccal patches of OLM

***3.3. In-vitro* Drug Release Study:**

Table 3 and Figure 5 show Cumulative % drug release of all formulations. From the drug release studies of all formulations, the maximum drug release (100.4 % at 2 min) was observed in the formulation F2 containing 500 mg of HPMC E5, 4ml of PEG 400 and 5mg of crospovidone. From the results of evolutionary parameters and in-vitro drug release study, F2 formulation was considered as optimum formulation.

3.4. Morphology of patch by SEM:

The SEM of F2 formulation showed smooth surface with uniform distribution of the drug in the formulation.

Time (min)	Cumulative % drug release					
	F1	F2	F3	F4	F5	F6
0	0	0	0	0	0	0
0.5	34.5 ± 0.81	38.6 ± 0.9	44.2 ± 0.80	48.3 ± 0.70	35.6±0.76	35.3±0.73
1	74.7 ± 0.71	88.1 ± 1.0	79.7 ± 1.40	82.7 ± 0.63	73.7±0.53	76.3±0.84
1.5	89.5 ± 0.56	93.4 ± 0.71	91.3 ± 0.59	94.2 ± 0.94	91.5±0.90	90±0.95
2	93.8 ± 0.49	100 ± 1.13	99.4 ± 0.88	94.9 ± 1.40	95.7±1.31	94.7±1.91
2.5	97.1 ± 1.31	102.7 ± 1.56	101.1 ± 1.23	97 ± 1.19	100.1±1.16	98.5±1.47
3	100.2 ± 0.58	103.5 ± 1.21	102.8 ± 1.09	100.5±1.13	101.9±1.37	101.6±1.32
3.5	101.8 ± 1.21	106.6 ± 1.41	103.7 ± 1.48	109.6±1.34	105.6±1.27	104.9±1.09
4	103.4 ± 1.92	108.1 ± 1.35	105.8 ± 1.90	112.3±1.26	111.7±1.13	109.4±1.56
5	104.0 ± 1.33	112.9 ± 1.60	106.9 ± 1.34	119.8±1.81	114.3±1.51	113.3±1.83

All values are expressed as mean ± S.D. (n=3)

Table 3: Cumulative % drug release profile of F1 to F6

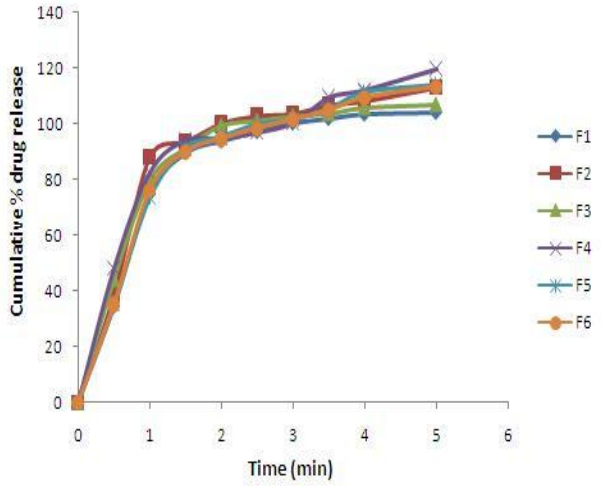

Figure 2: Cumulative % drug release of F1 to F6 formulations

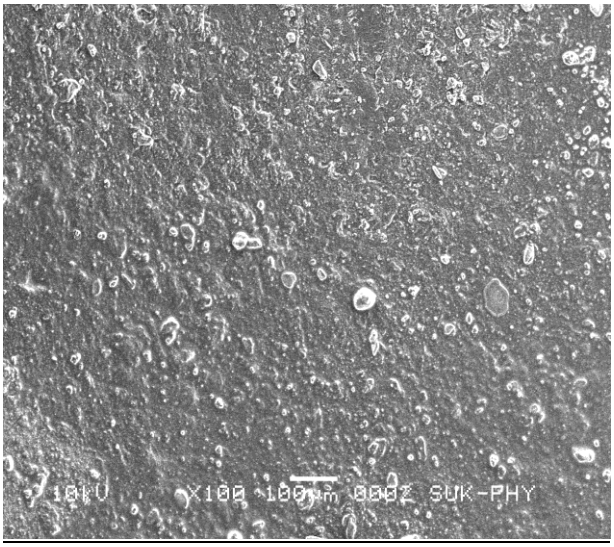

Figure 3: SEM of optimized formulation

3.5. Infrared spectrum analysis:

The compatibility of drug with polymer and other excipients is determined by IR study. Figure 4 shows IR spectrum of OLM, HPMC E5 and F2 formulation. IR spectrum showed that, characteristic peaks of OLM were found to be retained in spectrum of F2 formulation. Hence OLM was found to be compatible with HMPC E5.

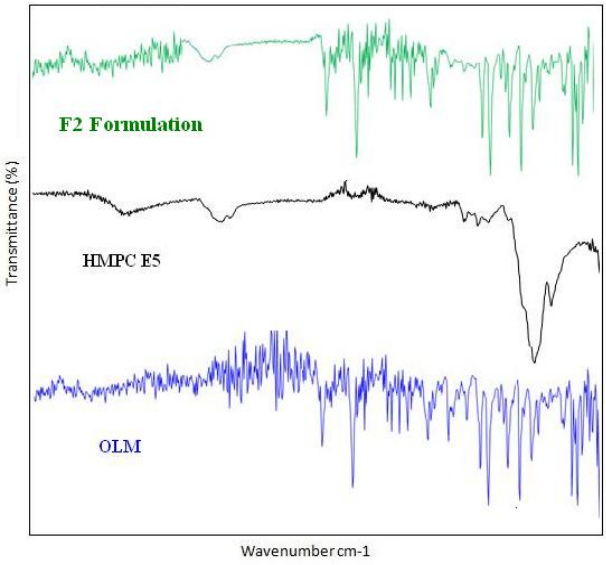

Figure 4: IR spectrum of OLM, HPMC E5 and F2 formulation

3.6. Stability studies:

After 3 month stability testing at 40^0C and 75% RH the patches was evaluated for drug content and other parameters. Results are shown in Table 4. From these results it was found that, formulations F2 is stable and retained their original properties with minor differences.

Formulation	Drug content (%)	Folding endurance	Weight (mg)	Surface pH	Disintegration time (sec)	% CDR in 2 min
F2	99.17±0.88	288±1.92	34.5±0.67	6.9±0.48	20±0.72	100.4±1.24

Table 4: Evaluation of optimized formulation after stability testing

4. CONCLUSION:

The results indicated that buccal patches are alternatives to oral fast dissolving tablets and can be helpful for the management of hypertension where quick onset of action is required. It was proved that HPMC E5 was the best film forming agent. The concentration of the Superdisintegrants in the formulation determines the drug release from the patches. As the concentration of crospovidone increases, the drug release from the patch also gets increased. It releases the drug up to 100% within 2 minute and treats the hypertensive patient immediately. This would improve patient compliance and disease management.

5. ACKNOWLEDGMENT:

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Conflict of Interest: None Declared

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