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Design and evaluation of thin film strip of polymer of Olmesartan for management of hypertension

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ABSTRACT: Background: Olmesartan medoxomil is an antihypertensive agent used for pediatric, elderly, psychiatric patients. **Aim:** The study was focused on design and evaluation of Thin Film Strip of Polymer of Olmesartan. **Method:** The solubility of Olmesartan was increased by β-Cyclodextrin complex by kneading method. The Olmesartan film was prepared by using polymers (HPMCK15M, and HPMCK4M) by solvent casting method. The prepared films were evaluated for Physical appearance, thickness, weight variation, drug content uniformity, moisture uptake, moisture loss, disintegration time, folding endurance and dissolution. **Result:** All the formulations were found to be transparent, having good folding endurance more than 300 times. The range of thickness and weight of film were from 0.20 to 0.26 mm and 0.64 to 0.76 mg respectively. The pH and drug content of all film formulations were in the range of 6.7 to 7 and 78.23 to 90.01 %. The pH value indicated that the film could be compatible with skin physiology. The moisture uptake and moisture loss was found to be very less and hence showed more flexibility and good plasticity of the film. The films were disintegrated rapidly (within 50 s) intact of citric acid with saliva. **Conclusion:** It can be concluded that the ultra-thin polymeric film of Olmesartan was successfully formulated by increasing the solubility of Olmesartan by forming inclusion complex with β-Cyclodextrin in 1:1 molar ratio and the optimized film formulation F5 containing Olmesratan and HPMCK4M in the ratio of 1:1.5 released the drug within a few seconds when placed in buccal mucosa.

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INTRODUCTION:

Polymeric film strips can be considered as a good option for patients, especially pediatric, geriatric and those patients who find difficulty in taking solid dosage form like tablet, capsule and find difficulty in inserting suppository [1,2]. In the 1970's, fast dissolving film emerged as a good option and an alternative drug delivery system with respect to solid dosage form [3].

Buccal cavity primarily consists of stratified squamous epithelium and is differentiated from the lamina propria

and submucosa tissue by an undulating basement membrane [4]. Permeability of buccal mucosa is around 4 to 4,000 times more than the skin surface and less than intestine. Thus buccal cavity is an appropriate site for permeation and absorption of many drugs [5]. The polymeric thin film can disintegrate rapidly within a few seconds when adhered to the buccal mucosa. The saliva enhances the permeation by permeating into pores and decreases disintegration. The significant merits of buccal films are avoiding hepatic first-pass metabolism and improved bioavailability [6].

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 which results in more and faster absorption of the drug through oromucosal tissues. Fast dissolving drug delivery system can be considered as an ideal dosage form to increase elderly and paediatric patient compliance because there are lots of variations in physiological factors [7,8].

Hot melt extrusion, semi-solid casting, solvent casting, rolling method and solid dispersion extrusion are used for the preparation of film. Absorption of drugs from GIT depends on their aqueous solubility.

Thus drug solubility can be increased by salt formation solubilization, complexation, particle size reduction, etc. Therefore, pharmaceutical research focuses on improving the oral bioavailability of active agents with respect to enhancing the solubility and dissolution rate of poorly water soluble drugs.

The β-Cyclodextrins complexation is used to enhance the solubility and stability of poorly soluble drugs in aqueous medium. The Cyclodextrins ring has a hydrophilic extrinsic and lipophilic core in which suitable sized organic molecules can form non-covalent inclusion complexes which leads to enhanced aqueous solubility and chemical stability.

The Olmesartan medoxomil (OLM) chemically named 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, is an antihypertensive agent practically insoluble in water and sparingly soluble in methanol [9-11].

In the present investigation, an attempt was made to formulate ultra-thin polymeric film of Olmesartan by first increasing its solubility by β-Cyclodextrin complex and then preparing Olmesartan thin polymeric film with objective that the film may release the drug within a few seconds when placed in buccal mucosa.

MATERIALS AND METHOD:

Chemicals and reagents:

Olmesartan (OLM) was obtained as a gift sample from Macleod's Pharmaceuticals Ltd, Mumbai, India. The β-Cyclodextrin, HPMCK15M, HPMCK4M, PVK 30, PEG 400, Aspartame, citric acid and other ingredients were purchased from HiMedia Lab Pvt Ltd, Mumbai. All other chemicals and reagents of analytical grade were procured from authorized dealers.

Instrumentation:

The research work was carried out on Shimadzu UV-visible Spectrophotometer (model UV-1800 series), which possesses a double beam double detector configuration with 1 cm quartz matched cell. All weighing was done on Shimadzu Analytical weighing balance. Equiptronics digital pH meter (model-EQ-610) was used to determine the pH. Labline dessicator were used for storage.

Phase-Solubility Studies:

Phase solubility study was carried out on the basis of the method reported by Higuchi and Connors [12]. It helped in the determination of the affinity between drug and carrier in aqueous solution. Olmesartan was added in excess quantity to conical flasks containing aqueous solution with the increased concentration of β-Cyclodextrin. The flask was shaken at 25 ºC for 48 h. The samples were filtered through Whatmann filter paper of pore size 0.45 µm. The filtrate was diluted and then assayed for Olmesartan concentration spectrophotometrically at 256 nm. The apparent stability constant was calculated from the phase solubility study and according to the equation as mentioned below.

$Kc = Slope/Intercept (1-slope)$ …….(1)

Preparation of Olmesartan-β-Cyclodextrin Inclusion Complex:

Based on phase solubility studies, Cyclodextrin-drug inclusion complex was prepared by kneading method. OLM and β-cyclodextrin was added in a ratio of 1:1 molar and was kneaded for 30 min using 40 % ethanol: water to maintain proper consistency. Then the product was dried at 40 ºC for 24 h and the resultant solid dispersion was sieved through 80 mesh and stored in a desiccator.

Preparation of thin film strip of Olmesartan:

For the preparation of film, the drug-β Cyclodextrin complex in 1:1 molar ratio, accurate weight of

HPMCK15M, HPMCK4M were taken in the drug polymer ratios of 1:1, 1:1.5 and 1:2. The polymer was hydrated in 4 ml of water in a separate beaker. Then the drug-β cyclodextrin complex was dissolved in methanol and the components were mixed by using the sonicator (Ats-4, Ultrasonic cleaner, Athena Technology, Mumbai). The methanolic solution was added in hydrated HPMC and kept on a magnetic stirrer (RSM-10A, Shimadzu Magnetic stirrer, Japan). The PEG 400, weighed an amount of aspartame, citric acid, menthol, tween 80 and peppermint oil were added in the above solution.

After continuous stirring for 3 to 4 h, the beaker was kept in vacuum to remove the entrapped air. The solution was poured in a petri-plate and kept in a hot air oven. After drying, the film was cut in size of 3 cm^2 and packed in an aluminium foil and kept in desiccators for evaluation.

Evaluation of Olmesartan Films:

Physical Appearance:

The prepared film was cut in accurate size and it was analysed for color, clarity, crystallisation of drug, flexibility and smoothness by feel or touch [13].

Thickness:

The thickness of each of 5 films of each type of formulation was measured using a Vernier calliper and the average thickness was measured.

Weight Variation:

Individual weight of 10 samples of each formulation was calculated by using the digital balance and the average weight was calculated [14].

Folding Endurance:

Folding endurance was used to check the flexibility of film and to determine the number of folds required to break the film or to develop the visible cracks. About 3 cm^2 film was folded repeatedly at the same place several times until a visible crack was observed [15]. The number of folding at which the film break was recorded as the folding endurance.

Drug Content Uniformity:

A film of area 3 cm^2 was dissolved in 100 ml of simulated saliva (pH 6.8) under occasional swirling. Then 1 ml solution was taken and diluted with simulated saliva pH 6.8 up to 10 ml, and the obtained solution was filtered through Whatman filter paper. The drug content was determined after proper dilution by using spectrophotometer at maximum wave length of 256 nm.

Surface pH:

The surface pH of the thin films was determined in order to know the side effects due to change in pH *in-vivo*. The pH was measured by dissolving a Olmesartan thin film in 1 ml of simulated saliva fluid and was calculated using pH meter [16].

Moisture Uptake:

The film sample was weighed and placed in a petri-plate containing 15 ml distilled water. Increase in film weight was determined at periodic time intervals until a constant weight was obtained. The hydration ratio of the film was calculated using the following formula.

$$\text{Hydration ratio} = \frac{Wt - W_0}{W_0} \times 100 \quad \ldots..(2)$$

Where, Wt = Final weight and W_0 = Initial weight.

Moisture Loss:

The percent moisture loss was measured by placing Olmesartan thin film in desiccators containing anhydrous calcium chloride. The film was taken and reweighed after three days [17]. The percent moisture loss was calculated using the following formula.

$$\text{Moisture loss} = \frac{W_0 - Wt}{W_0} \times 100 \quad \ldots\ldots(3)$$

Where, W_0 = Initial weight and Wt = Final weight.

Disintegration Test:

It is determined in a test tube of 10 ml simulated saliva pH 6.8 with swirling at every 10 s on a vortex mixer [17].

In-vitro drug release studies:

Dissolution test was carried out in a beaker containing 30 ml of simulated salivary fluid (pH6.8) as a dissolution medium, maintained at a temperature of 37±0.5 °C on a magnetic stirrer. The medium was stirred at 100 rpm. Aliquots (1 ml) of dissolution medium were withdrawn at 1 min interval and the same volume was replaced with blank salivary fluid which was maintained at the same temperature. Samples were assayed spectrophotometrically at 256 nm [17].

RESULTS AND DISCUSSION:

Olmesartan medoxomil has poor aqueous solubility which was increased by forming an inclusion complex with β-cyclodextrin. From the phase solubility study, it was found that 1:1 molar ratio of Olmesartan-β cyclodextrin complex showed more aqueous solubility

Table 1. The formulation design Olmesartan thin film strip.

Ingredients	F1 (1:1)	F2 (1:1.5)	F3 (1:2)	F4 (1:1)	F5 (1:1.5)	F6 (1:2)
OLM+β-CD	714	714	714	714	714	714
HPMCK15M	714	1071	1428	-	-	-
HPMCK4M	-	-	-	714	1071	1428
PEG 400	1.5	1.5	1.5	1.5	1.5	1.5
Aspartame	1	1	1	1	1	1
Citric Acid	10	10	10	10	10	10
Menthol	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.
Tween 80	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.
Methanol	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.
PVPK30	107	107	107	107	107	107
Peppermint Oil	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.
Water	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.

Olmesartan+β-cyclodextrin complex and q.s. is quantity sufficient.

Table 2. The physical appearance, thickness, weight uniformity, folding endurance and surface pH data of films.

Evaluation Parameter	F1	F2	F3	F4	F5	F6
Physical Appearance	Transparent	Transparent	Transparent	Transparent	Transparent	Transparent
Thickness (mm)	0.20	0.26	0.25	0.20	0.25	0.22
Weight uniformity (mg)	0.70	0.76	0.66	0.64	0.66	0.65
Folding Endurance	+300 times	+300 times	+300 times	+300 times	+300 times	+300 times
Surface pH	6.8	6.9	7	6.8	7	6.7

Table 3. The drug content, moisture uptake, moisture loss and disintegration time data of films.

Evaluation Parameter	F1	F2	F3	F4	F5	F6
Drug Content (%)	85.45	85.02	78.23	87.21	90.01	82.33
Moisture uptake	2.85	1.31	1.51	1.56	1.51	1.56
Moisture loss	1.21	1.11	1.11	1.32	1.01	1.21
Disintegration time (s)	40	42	44	40	35	50

and hence six fast dissolving films were prepared with different concentration of HPMCK15M, HPMCK4M along with the other ingredients. Solvent casting was found to be an efficient method for successful manufacturing of films.

All film formulations were found to be transparent, flexible, smooth, and uniform without crystallisation of the drug. The thickness of all batches of films ranged from 0.20 to 0.26 mm, which revealed that uniform thickness of all film was achieved (Table 2). The weight of Olmesratan film varied from 0.64 to 0.76 mg (Table 2). The result of weight of films showed that all films obtained almost uniform weight. The folding endurance of all films was found to be more than 300, which revealed that the films were much flexible. The pH of all six formulations was in the range of 6.7 to 7, this value simulating with the buccal pH, revealing compatibility of formulation with biological systems (Table 2).

The drug content of all the six Olmesartan films was in the ranges of 78.23 to 90.01 % (Table 3). The film formulation F5 showed maximum drug content (90.01 %), whereas formulation F3 exhibited minimum (78.23

%) drug content. The moisture uptake and moisture loss was found to be very less and hence showed more flexibility and good plasticity of the film. The low moisture content may assist in exhibiting the more stability of film. The time required to disintegrate the film was in the range of 35 to 50 s (Table 3). The film disintegrated rapidly due to addition of citric acid and on coming in contact with saliva (Table 3).

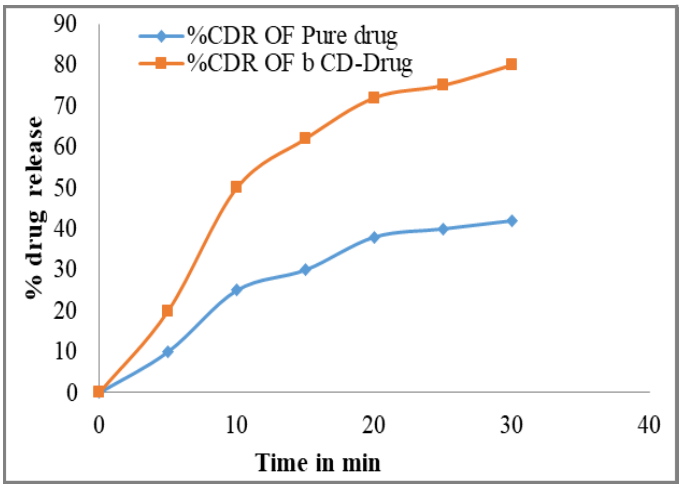

Fig 1. The solubility studies of Olmesartan and Olmesartan-β Cyclodextrin Complex.
CDR – Cumulative drug release, b CD – beta cyclodextrin.

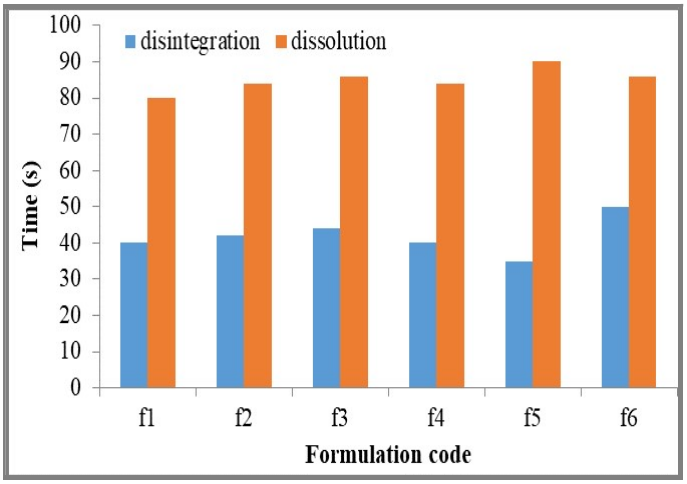

Fig 2. The disintegration and dissolution data comparison between various films.

The *in-vitro* dissolution data of various Olmesartan films has shown in Fig 2 and 3. All batches of film released drugs in ranges of 83 to 90 %. All films released drugs very quickly within 2 min. Hence from the given data it was found that F5 formulation showed good disintegration time as well as drug release profile.

CONCLUSION:

It can be concluded that the ultra-thin polymeric film of Olmesartan was successfully formulated by increasing the solubility of Olmesartan by forming inclusion complex with β-Cyclodextrin in 1:1 molar ratio depending on the phase solubility studies and then preparing Olmesartan thin polymeric film for the management of hypertension which released the bioactive fragment within a few seconds when placed in buccal mucosa.

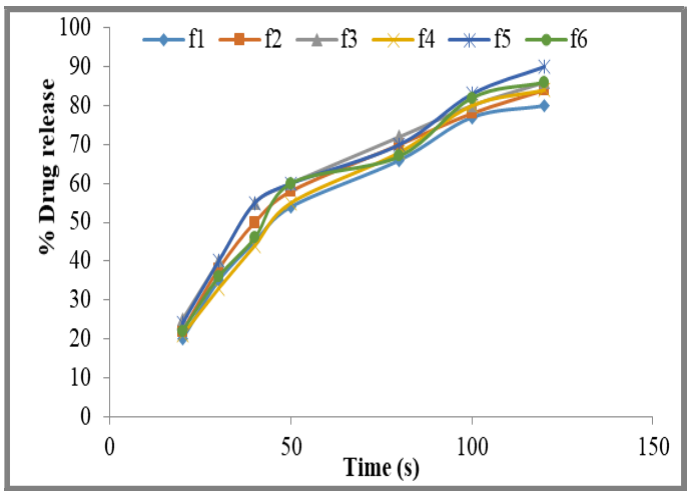

Fig 3. The drug release profile from various films.

Thus the Olmesartan thin polymeric film F5 containing the Olmesratan and HPMCK4M in the ratio of 1:1.5, was found to be optimized formulation as it possesses the highest drug content with best disintegration and drug release profile. Hence this formulation could be successfully used for safe and effective management of hypertension.

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