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Formulation and Evaluation of Olmesartan Medoxomil Mouth Dissolving Film

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ABSTRACT:

The oral route is the most preferred route, though preoral administration of drug has disadvantage like hepatic first pass metabolism and enzymatic degradation within the GI tract however trans mucosal routes of drug delivery (i.e. Mucosal lining of nasal, rectal, vaginal, ocular, & oral cavities) offer distinct advantage over preoral administration because mucosa are permeable and well supplied with vascular and lymphatic drainage. Their other advantages include bypass of first pass effects and avoidance of pre-systematic elimination within GI tract. The present investigation highlights the formulation and evaluation of mouth dissolving films of Olmesartan Medoxomil, prepared by solvent casting technique. Film made up of different polymers but combination of HPMC E15 and PVA was optimized as final formulation.

KEYWORDS: Olmesartan Medoxomil,β-Cyclodextrins, HPMC E15, PVA, Mouth Dissolving films, Solvent casting technique.

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INTRODUCTION:

Mouth dissolving films offers an attractive route for systemic drug delivery. The improved systemic bioavailability results from bypassing first pass effect and better permeability due to a well supplied vascular and lymphatic drainage Also large surface area of absorption, easy ingestion & swallowing, pain avoidance make the oral mucosa a very attractive and feasible site for systemic drug delivery[1,2,3,4].

The delivery system consist of a very thin oral strip, which is simply based on the patient's tongue or any oral mucosal tissue, instantly wet by saliva the film rapidly hydrates and adheres onto site of application. It then disintegrates and dissolves to release the medication[3,5,6,7].

The objective of present study is to develop the MDF of an antihypertensive drug, Olmesartan Medoxomil an angiotensin II receptor antagonist and thereby imparting the significance, ideal characteristics and various aspects related to mouth dissolving film formulation as a superior dosage form in treatment of hypertension and to improve the patient compliance[8,9,10,11]. This work is used to develop MDF of drug candidate to improve bioavailability, dissolution time, disintegration time and patient compliance.

The present investigation highlights the formulation and evaluation of mouth dissolving films of Olmesartan Medoxomil. The films were prepared by solvent casting technique using polymers of hydroxy propyl methyl cellulose (HPMC) –E15 and polyvinyl alcohol (PVA).

OBJECTIVES:

The objective of present study is to develop mouth dissolving films of Olmesartan Medoxomil for better patient compliance and to provide effective mode of treatment to the patient who is suffering from hypertension.

But the major problem with this drug is - it's poor solubility which can be enhanced by solubility enhancing approach like

1. by complexation method
   - With β-CD

MATERIALS AND METHODS:

Olmesartan Medoxomil,was gift sample from CTX life science,Surat. All other ingredients were obtained from purvi laboratory. All ingredients were of analytical reagent grade.

Solvent Casting Method:

The weighed quantities of polymers were kept for swelling in distilled water and dissolved (heated, if necessary). The drug and sweetner were dissolved in distilled water and added to the above mentioned polymer solution along with plasticizer, mixed thoroughly to form a homogenous mixture. The volume was made up to 10 ml with distilled water. Entrapped air bubbles were removed by applying vacuum.[2,4]

SOLUBILITY STUDIES:

1.1 Phase solubility studies:[12,13]

Phase-solubility studies were carried out according to the method reported by Higuchi and Connors . It Permits the evaluation of the affinity between the carrier and drug in aqueous solution and to know the stable inclusion complex. An excess amount of olmesartan was added to an aqueous solution into a conical flask with increase in concentration of β-cyclodextrins (2-10mm). These flasks were kept on sonicator at room temperature for 48 hours. Then the samples were filtered through a Whatman filter paperwith a pore size 0.45 µm.

Table no.1-Phase solubility data

Conc. of β-cd (mm/l)	Absorbance	Conc (µg/ml)	Amount of drug dissolved (mg)	Conc. of olmesartan (mm)
2	0.327	9.97	0.997	0.00178
4	0.389	11.7	1.17	0.00209
6	0.501	15.08	1.508	0.00269
8	0.61	18.29	1.829	0.00333
10	0.744	22.23	2.223	0.00397

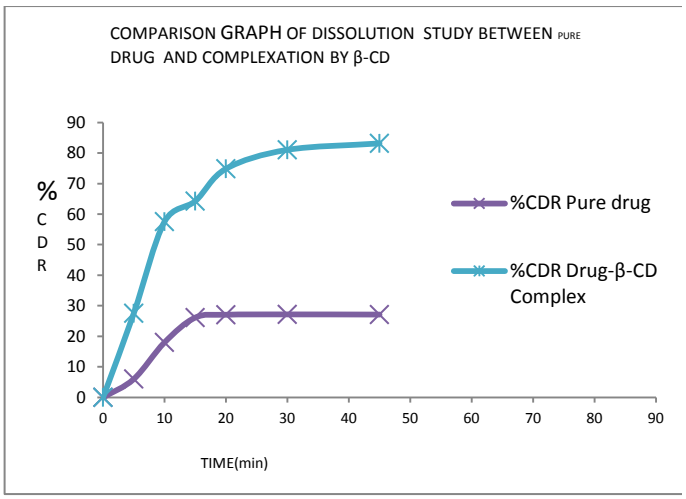

Figure 1- Dissolution Study between drug and complex

The filtrate was diluted and assayed for OLM content spectrophotometrically at 253 nm. Phase Solubility result is shown in Table no.1 and phase solubility diagram is shown in figure 1.

2. FORMULATION AND DEVELOPMENT:

2.1 Drug Calculation:

Optimum dose of olmesartan Medoxomil = 10 mg

So, 2cm*2cm = 4 cm^2 containing 10 mg of olmesartan medoxomil

Now ,the area of petridish = $\pi r^2 = (3.14) * (4.3)2$

=58.05 cm^2

4cm^2 containing 10 mg of olmesartan medoxomil

∴58.05 cm2 containing = $\frac{10 * 58.05}{4}$

= 145.125 mg of olmesartan medoxomil

To make drug-β CD Complexation,amount of olmesartan medoxomil and β-CD were taken according to 1:1 molar ratio

So,total amount of complex = 1135+558.59

=1693.59 mg of complex

Now ,558.59 mg of olmesartan medoxomil in 1693.59 mg of complex

∴10 mg of olmesartan medoxomil in 30.31 mg of complex.

So, for assay , 30.31 mg drugcomplex was taken

Assay = 86.1%

So, according to assay 8.61 mg of olmesartan medoxomil in 30 mg complex

So,10 mg of olmesartan medoxomil in 34.843 mg complex

So, according to area of petridish drug complex =

$\frac{58.05 * 34.843}{4}$ = 505.65 mg of complex was taken.

Table 2 Composition of mouth dissolving film: Composition of F1 to F10 Batches:

Ingredients	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10
API(Olmesartan medoxomil)+β-CD Complex	505.65	505.65	505.65	505.65	505.65	505.65	505.65	505.65	505.65	505.65
PVA	450	450	150	150	150	150	-	450	-	-
HPMC E15	-	-	300	300	300	300	450	-	-	-
PVP K30	-	-	-	-	-	-	-	-	450	-
Guar gum	-	-	-	-	-	-	-	-	-	450
Glycerin	120	120	-	120	-	-	-	-	-	-
PG	-	-	-	-	120	-	-	-	-	-
PEG	-	-	120	-	-	-	120	120	120	120
DBP	-	-	-	-	-	120	-	-	-	-
Citric acid	20	20	20	20	20	20	20	20	20	20
Aspartame	5	5	5	5	5	5	5	5	5	5
Peppermint oil	q.s	q.s	q.s	q.s	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	q.s	q.s	q.s	q.s
Water	-	q.s	-	q.s	-	q.s	-	q.s	-	q.s
Methanol	q.s	-	q.s	-	q.s	-	q.s	-	q.s	-
Total	1100	1100	1100	1100	1100	1100	1100	1100	1100	1100

Table no.3- Composition of mouth dissolving film F11 to f16 batches:

Ingredients	F11	F12	F13	F14	F15	F16
API(Olmesartan medoxomil)+β-CD Complex	505.65	505.65	505.65	505.65	505.65	505.65
PVA	300	300	-	400	-	400
HPMC E15	150	-	300	-	400	-
PVP K30	-	150	150	-	-	-
Guar gum	-	-	-	50	50	50
Glycerin	-	-	-	-	-	-
PG	-	-	-	-	-	-
PEG400	120	120	120	120	120	120
DBP	-	-	-	-	-	-
Citric acid	20	20	20	20	20	20
Aspartame	5	5	5	5	5	5
Peppermint oil	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
Water	-	q.s	-	q.s	-	q.s
Methanol	q.s	-	q.s	-	q.s	-
Total	1100	1100	1100	1100	1100	1100

F7-F10:Polymer optimization

F11-F16:Polymer ratio optimization All ingredients were in mg

F1-F2:Solvent optimization

F3-F6:Plasticizer optimization

3. EVALUATION PARAMETERS:

1. Physical appearance:[1,3,4,6]

Film was visually inspected for color, clarity, flexibility and smoothness by feel or touch.

2. Weight uniformity and Thickness:[1,3,4,7]

The assessment of weight and film thickness was done in 10 different randomly selected films from each batch. Films were directly weighed on a digital balance and film thickness was measured using a screw gauge.

3. Drug Content Uniformity:[1,3,4,7]

Drug content uniformity was determined by dissolving the 4cm^2 film in 100 ml of Simulated saliva (pH 6.8) under occasional shaking. Then 1 ml solution was taken and diluted with simulated saliva pH 6.8 up to 10 ml, and the resulting solution was filtered through Whatmanfilter paper. The drug content was determined after proper dilution at spectrophotometer.

Endurance:[1,3,4,7]

The folding endurance of the films was determined by repeatedly folding one film at the same place till it broke or folded up to 300 times, which is considered satisfactory to reveal good film properties.The number of times of film could be folded at the same place without breaking gave the value of the folding endurance. 5. Surface pH:[1,2,7]

The pH was determined by dissolving a film in 2 ml of pH 6.8 simulated saliva and then pH of the obtained solution was measured by pH meter.

6. Tensile Strength:[1,2,6,7]

Tensile strength was measured by using tensilometer.

7. % Elongation:[1,2,6,7]

$$\frac{\text{Final length of strip-Initial length}}{\text{Initial length}} \times 100$$

8. Tear resistance:[6,7]

It is calculated by calculating Stress applied to tear the film.

9. Disintegration test :[5,7]

It is determined in a glass dish of 25 ml simulated saliva pH 6.8 with swirling at every 10 sec. The disintegration time is the time ,when the film starts to break.

10. In vitro release studies:[14]

Dissolution was carried out in a beaker containing 30 ml of

simulated salivary fluid(pH6.8) as a dissolution medium, maintained at 37±0.5ºC.The medium was stirred at 100 rpm.Aliquots (1 ml)of dissolution medium were withdrawn at 1 min interval.Same amount of volume was replaced with fresh medium.Samples were assayed spectrophotometrically at 253 nm.

Table no.4-Evaluation parameter of mouth dissolving film F1 to F10 % F11 to F16:

Evaluation parameter	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10
Appearance	Bad	Good	Good	Average	Bad	Bad	Good	Good	Bad	Bad
Weight uniformity	70.00 mg	72.23 mg	45.07	57.23	80.78	70.02	69.51	75.68	72.34	55.04
Thickness (mm)	0.17 mm	0.15 mm	0.2	0.19	0.17	0.16	0.17	0.16	0.19	0.14
Folding endurance	67	90	175	86	47	75	9	150	30	15
Surface pH	7	7	7	7	7	7	7	7	7	7
Tensile strength(gm)	780	800	800	550	100	240	80	800	120	20
% Elongation	10.71	13.26	15.35	13.63	2.45	6.23	1.5	13.78	7.05	2.09
Tear resistance (gm/cm^2)	195	200	200	137.5	25	60	20	200	30	5
Disintegration time(sec)	45	57	37	43	56	40	30	37	43	75
%Assay	90.14	74.65	85.89	70.21	68.34	60.02	84.89	85.34	82.61	65.40

Evaluation parameter	F11	F12	F13	F14	F15	F16
Appearance	Good	Good	Bad	Bad	Bad	Bad
Weight uniformity	71.3 mg	70.5mg	78.29mg	61.65mg	72.2mg	72.65mg
Thickness	0.17mm	0.18mm	0.21mm	0.14mm	0.16mm	0.20mm
Folding endurance	201	220	10	156	178	26
Surface PH	7	7	7	7	7	7
%Elongation	12.22%	15.13%	3.29%	10.14%	9.17%	6.50%
Tear resistance(gm/cm^2)	150	200	10	115	130	80
Tensile strength(gm)	600	800	40	460	520	320
%Assay	91.32%	90.07%	63.33%	80.43%	82.21%	61.78%
Disintegration time	30sec	44sec	63sec	67sec	70sec	59sec

Table no.5- *IN VITRO* DISSOLUTION STUDY

Formulation code	Time (min)	%CDR
F1	5	100.07
F2	5	75.07
F7	4	83.37
F8	4	80.71
F9	5	77.05
F10	6	51.35
F11	5	89.00
F12	5	87.31
F13	6	55.83
F14	6	77.01
F15	6	79.85
F16	6	58.80

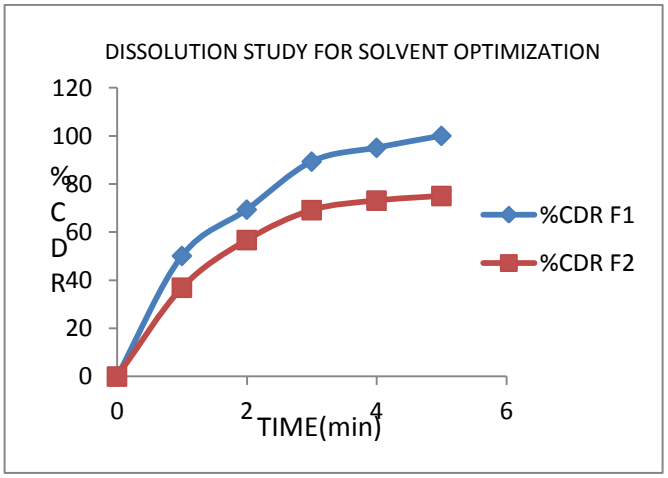

Figure no.3-Dissolution study of F1 to F2 Batch

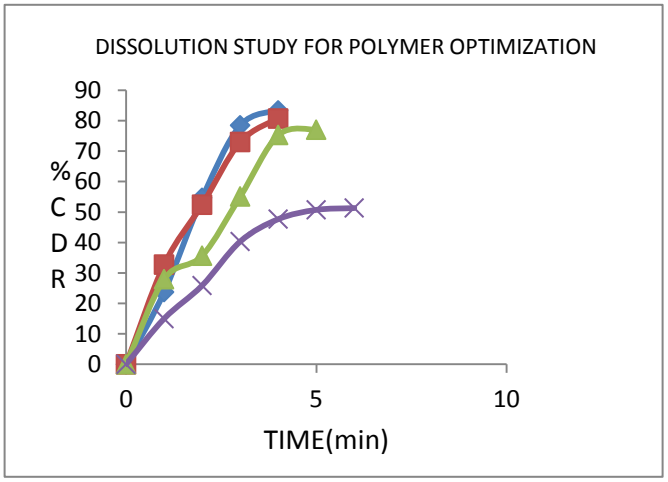

Figure no.4-Dissolution study of F7 to F10

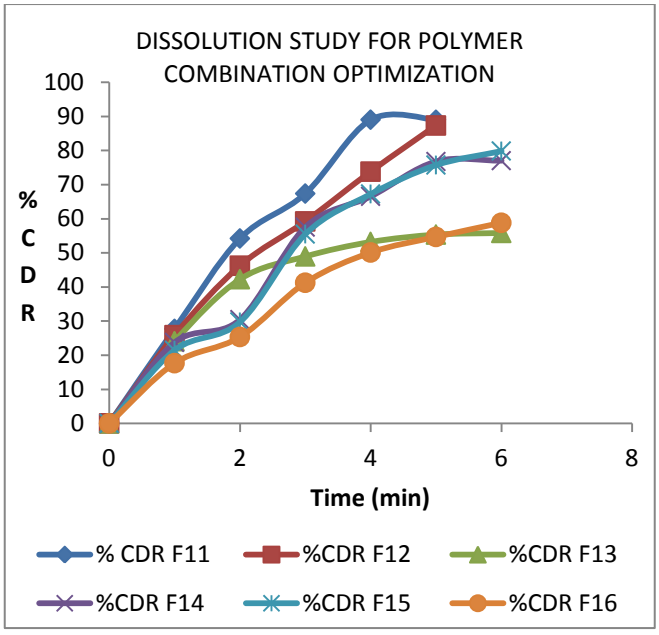

Figure no.5-Dissolution study of F11 to F16

RESULT AND DISCUSSION:

Olmesartan Medoxomil is angiotensin II receptor which reduces vasoconstriction and the secretion of aldosterone. This lowers blood pressure by producing vasodilation, and decreasing peripheral resistance.Olmesartan medoxomil has poor aqueous solubility which was enhanced by using complexation using β-CD. The combination of HPMC E15 and PVA was found to be good polymer combination with respect to its physical and mechanical property and drug releasing property.

CONCLUSION:

From the experiment, It can be concluded that solubility of Olmesartan medoxomil was increased by using complexation with β-CD. Among all batches F11 was found to be an optimized formulation .

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