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Formulation, development and evaluation of transdermal patches of Olmesartan Medoxomil

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Abstract

Olmesartan medoxomil is indicated for the treatment of hypertension and may be used alone or in combination with other antihypertensive agents. The present work deals with the development of transdermal patches of olmesartan medoxomil. The formulated patch was evaluated.

Key-Words: Transdermal patch, Olmesartan medoxomil, Hypertension

Introduction

Delivering medicine to the general circulation through the skin is seen as a desirable alternative to taking it by mouth. Patients often forget to take their medicine, and even the most faithfully compliant get tired of swallowing pills, especially if they must take several each day. Additionally, bypassing the gastrointestinal (GI) tract would obviate the GI irritation that frequently occurs and avoid partial first-pass inactivation by the liver. Further, steady absorption of drug over hours or days is usually preferable to the blood level spikes and troughs produced by oral dosage forms.

These advantages are offered by the currently marketed transdermal products. One of the most successful, the nicotine patch, releases nicotine over sixteen hours, continuously suppressing the smoker's craving for a cigarette. The scopolamine patch is worn behind the ear and releases the alkaloid for three days, preventing motion sickness without the need to swallow tablets periodically. The fentanyl patch acts for seventy-two hours, providing long-lasting pain relief. And an estrogen–progestin contraceptive patch needs to be applied only once a week, a boon for women who find it onerous to take one pill every day.

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The transdermal route is indeed desirable, but there is one small obstacle: whereas the function of the GI tract is to render ingested material suitable for absorption, the skin's function is to keep things out of the body.

Olmesartan medoxomil ($C29H30N6O_6$)is a white to light yellowish-white powder or crystalline powder with a molecular weight of 558.59. It is practically insoluble in water and sparingly soluble in methanol. It is indicated for the treatment of hypertension and may be used alone or in combination with other antihypertensive agents. Literature review indicates that till yet no work was done in formulating transdermal patches using this drug therefore, the present work was undertaken.

Material and methods

Drug solubility determination

Solubility of OLM was determined in different solvents at 25˚ C temperature as per IP

Construction of Pseudo-ternary Phase Diagrams

In order to find out the concentration range of components for existence range of microemulsion, pseudo-ternary phase diagrams were constructed using water titration methods at room temperature i.e. 25^0C. Three phase diagrams were prepared with the 1:1, 2:1 & 1:2 weight ratios of Tween 80 to isopropyl alcohol respectively. For each phase diagram at specific surfactant/ cosurfactant weight ratio, the ratios of isopropyl alcohol to the mixture of surfactant/ cosurfactant were varied as 0.05: 0.95, 0.1:0.9, 0.15:0.85, 0.2:0.8, 0.25:0.75, 0.3:0.7, 0.35: 0.65, 0.4:0.6, 0.45:0.55, 0.5:0.5. The mixtures of oil, surfactant and cosurfactant at certain weight ratios were diluted with water drop wise, under moderate

magnetic stirring. After being equilibrated, the mixture were assessed visually and determined as being microemulsions, crude emulsions, or gels.

Microemulsions formulations

Preparation of Olmesartan medoxomil loaded microemulsions

Olmesartan medoxomil was added to the mixture of oil, surfactant and co-surfactant with varied components ratios as described in the table and then an appropriate amount of water was added to the mixture drop by drop and the microemulsion containing Olmesartan medoxomil obtained by stirring the mixture at room temperature. All microemulsions were stored at room temperature.

Formulation of transdermal patches of microemulsion loaded olmesartan medoxomil

Transdermal patches of Olmesartan medoxomil were prepared by solvent casting technique employing Ethylcellulose and Polyvinylpyrollidone for fabricating polymeric matrix into which drug has to be dispersed. We have taken 1:1 ratios of Ethylcellulose and Polyvinylpyrollidone is an ideal ratio for fabrication. To this transdermal patch, dibutyl phthalate added in the formulation as a plasticizer and without any permeation enhancer. The casting solutions were prepared by dissolving appropriate polymers, plasticizer in suitable vehicle using a magnetic stirrer. The drug was added slowly to the solution and dissolved by continuous stirring for 30 min. After uniform solution was obtained, it was poured uniformly on a glass petri dish. The mould was kept on a horizontal surface. About 10 ml of the solution was poured on the petridish (63.64 cm^2 area). The rate of evaporation was controlled by inverting a funnel over the mould. After 24 h, the dried cast films were then detached from the petri dish and films were cut to generate transdermal patch of 2.0 cm in diameter with 0.2mm in thickness. The formulated patches were stored in dessicators Table 5.

Evaluation of Transdermal Patches

Physical appearance, Weight & Thickness

The weight, thickness and physical consistency of the films were observed immediately after formulation. On achieving the desired characteristics of the film, the same was also subjected to storage for one month at normal room temperature conditions. This was done to determine the effect of storage conditions on the physical nature of the prepared films.

Tensile strength

It is measured in kg/cm2 by enacting the weight onto the specified area of film till it breaks. This was done to find out the flexibility/ elasticity of the patch/film.

Folding endurance

The folding endurance (FE) is defined as the number of folds required to break any polymeric film. The folds on the patch/film have to be made at the same point, till it breaks. It was measured manually by cutting a strip of patch of uniform size (4 x 3 cm) and repeatedly folded at the same place till it broke. The number of folds a film/patch can sustain will dictate its Folding endurance. (Table 6)

Percent elongation

It is defined as the ratio between the length of film/patch in normal condition and to the stress condition. Here, stress conditions would be stated as stretching the film/patch to the point till it breaks down. Measuring the length of the intact patch before breaking and combined length of the broken pieces after stress condition is necessary to estimate the percent elongation. (Table 6)

Water vapor transmission

The film was fixed over the edge of the glass vial containing 3 gm of fused calcium chloride as the desiccant by using an adhesive. Then the vial was placed in a desiccators containing saturated solution of potassium chloride. The vial was taken out periodically and weighed for a period of 72 h. The experiment was performed in triplicate and the average values are reported in Table 6.

Percent moisture absorption

The moisture absorption study of various films was carried out at 63% relative humidity. The film of known thickness was fixed over the edge of the glass vial containing 3 gm of fused calcium chloride as desiccant by using an adhesive. Then the vial was weighed & placed in a desiccators maintained at the 63% & relative humidity. The vial was taken out periodically and weighed for a period of 72 h. The experiment was performed in triplicate and the average values are reported in Table 6.

Percent moisture loss

The film of known thickness was fixed over the edge of the glass vial using an adhesive. Then the vial was weighed and kept in desiccators containing 10 gm of calcium chloride as desiccant. The vial was taken out periodically and weighed for a period of 72 h and the values were calculated and reported. (Table. 6)

Accelerated temperature stability testing

The films were stored at different temperature conditions of 4, 25& 40^0C to ascertain the effect of extreme temperature variation on the physical consistency and drug content of the transdermal patch. Thereafter all the physicochemical evaluation tests were performed over them. The drug content study was

also carried out on the stored transdermal films. (Table 7)

Content uniformity test

10 patches are selected and content is determined for individual patches. If 9 out of 10 patches have content between 85% to 115% of the specified value and one has content not less than 75% to 125% of the specified value, then transdermal patches pass the test of content uniformity. But if 3 patches have content in the range of 75% to 125%, then additional 20 patches are tested for drug content. If these 20 patches have range from 85% to 115%, then the transdermal patches pass the test.

Drug content determination

An accurately weighed portion of film (about 100 mg) is dissolved in 100 ml of suitable solvent in which drug is soluble and then the solution is shaken continuously for 24 h in shaker incubator. Then the whole solution is sonicated. After sonication and subsequent filtration, drug in solution is estimated spectrophotometrically by appropriate dilution.

Flatness

A transdermal patch should possess a smooth surface and should not constrict with time. This can be demonstrated with flatness study. For flatness determination, one strip is cut from the centre and two from each side of patches. The length of each strip is measured and variation in length is measured by determining percent constriction. Zero percent constriction is equivalent to 100 percent flatness.

$$\% \text{ constriction} = \frac{I_1 - I_2}{I_1} \times 100$$

I_2 = Final length of each strip

I_1 = Initial length of each strip

***In-vitro* permeation studies**

After removing the hairs from abdominal surface with scissor and depilatory cream, freshly excised goatskin with intact stratum corneum was mounted on the receptor compartment of the diffusion cell. The transdermal films measuring 3 x 3 cm2 area were placed over the skin in intimate contact with stratum corneum. A sheet of aluminum foil was kept onto the surface of transdermal film, which acts as the backing membrane & as well as fix the film properly with the skin.

The receptor compartment was filled up with the solvent system (elution medium) chloroform and was checked to avoid air-bubble. The diffusion cell was then kept on the magnetic stirrer at 37° for constant stirring throughout the study with the maintenance of sink condition. Aliquots of 1ml solvent from the receptor compartment were withdrawn periodically up to 24 h and, after making suitable dilution, analyzed spectrophotometrically at 360 nm against blank reagent within stability period of 60 min. Each formulation was carried out in triplicate. The cumulative amount of drug released /cm2 was then plotted against time1/2 and the slope of the linear portion of the plot was estimated as steady state flux (mg/cm^2/ h) (Table 7).

Results and Conclusion

The formulated transdermal patch of Olmesartan medoxomil was evaluated for thickness, tensile strength, folding endurance and content uniformity. Thickness of transdermal patch was measured by micrometer screw gauge. The thickness of the films varies between 0.232 ± 0.45mm to 0.252 ± 1.64. The tensile strength of the films was found vary with the nature of the polymer. It was found to vary between 2.190-3.687 kg/cm^2. All the physical properties of the transdermal patches were in acceptable limits. The transdermal patches containing Ethyl cellulose: PVP showed higher tensile strength as compared to patches containing HPMC: PVP. The Tensile strength of transdermal patches prepared from ethyl cellulose and HPMC: PVP also showed lower values which suggest that addition of polyvinyl pyrrolidone and ethyl cellulose matrix increases tensile strength of patches. Folding endurance of the transdermal patches was measured and it was varied between more then 150 to 200. Folding endurance of the transdermal patches was in acceptable limits.

The drug content uniformity was determined for all the six formulations by spectrophotometric method. The drug content for prepared batches of transdermal patches (10 patches in each batch) of Olmesartan medoxomil varies between 91%w/w to 103%w/w of drug. It was considered that the drug is dispersed uniformly throughout the film.

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Table 1: Solubility profile of drug

Water	0.1N HCl	0.1 N NaOH	Methanol	Cyclohexane	Ethanol
-	-	+	+	+	+

Table 1: Various proportion for pseudo-tertiary phase

Oleic acid (ml)	Surfactant/Co-surfactant (1:1) (ml)	Water (ml)
0.05	0.95	50
0.1	0.9	1.5
0.15	0.85	0.9
0.2	0.8	0.9
0.25	0.75	0.7
0.3	0.7	0.5
0.35	0.65	0.5
0.4	0.6	0.4
0.45	0.55	0.3
0.5	0.5	0.2

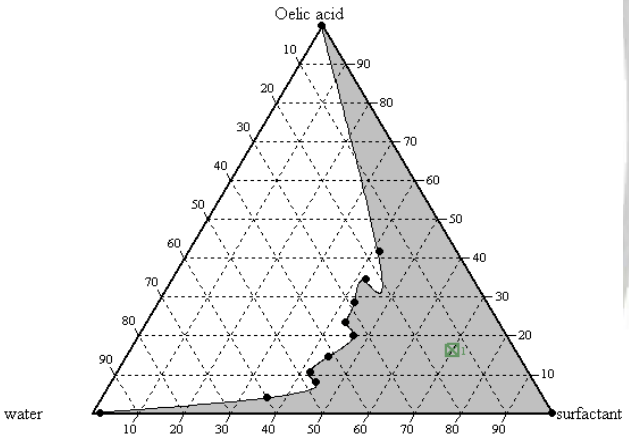

Fig. 1: Pseudo-ternary phase diagram of Oleic acid, Tween 80 and Isopropyl alcohol using 1:1 surfactant / co-surfactant ratio

Table 2: Various proportion for pseudo-tertiary phase

Oleic acid (ml)	Surfactant/co-surfactant (2:1) (ml)	Water (ml)
0.05	0.95	50
0.1	0.9	1.3
0.15	0.85	1.1
0.2	0.8	0.9
0.25	0.75	0.8
0.3	0.7	0.6
0.35	0.65	0.5
0.4	0.6	0.3
0.45	0.55	0.2
0.5	0.5	0.1

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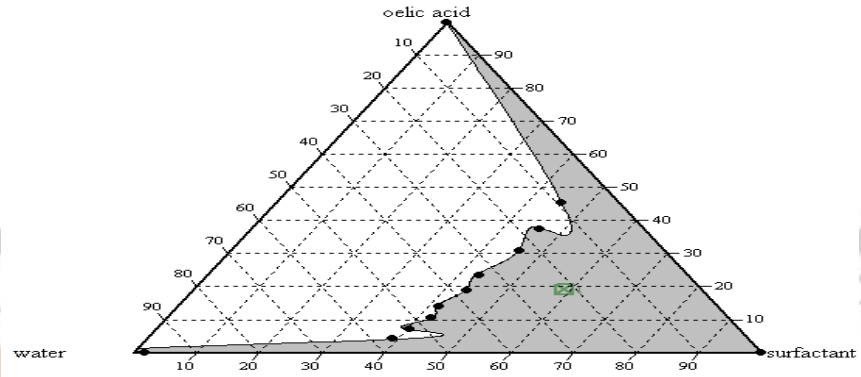

Fig. 2: Pseudo-ternary phase diagram of Oleic acid, Tween 80 and Isopropyl alcohol using 2:1 surfactant / co-surfactant ratio

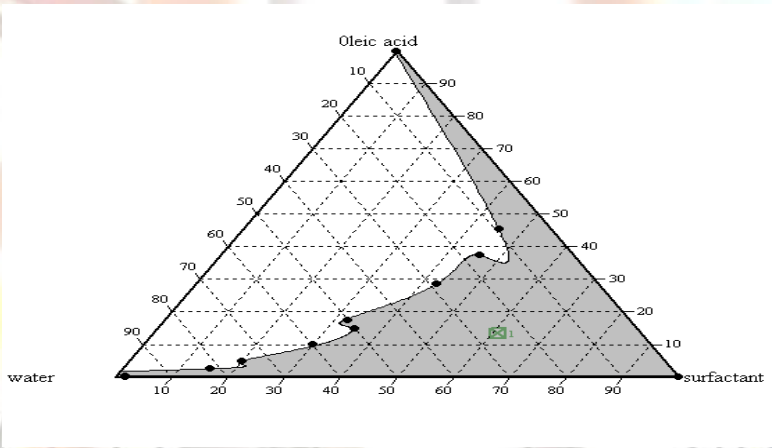

Fig. 3: Pseudo-ternary phase diagram of Oleic acid, Tween 80 and Isopropyl alcohol using 1:2 surfactant / co-surfactant ratio

Table 3: Various proportion for pseudo-tertiary phase

Oleic acid (ml)	Surfactant/co-surfactant (1:2) (ml)	Water (ml)
0.05	0.95	50
0.1	0.9	50
0.15	0.85	4.5
0.2	0.8	3
0.25	0.75	1.5
0.3	0.7	1
0.35	0.65	1
0.4	0.6	0.4
0.45	0.55	0.2
0.5	0.5	0.1

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Table 4: Preparation of Olmesartan medoxomil loaded microemulsions

Vehicle	Olmesartan medoxomil (gm)	Oleic acid (gm)	Tween 80 (ml)	Isopropyl alcohol (ml)	Water up to (ml)
A	0.2	0.2	4	2	10
B	0.2	0.4	2	1	10
C	0.2	0.4	3	1.5	10
D	0.2	0.4	4	2	10

Table 5: Composition of various formulations of matrix type transdermal patches of Olmesartan medoxomil

Code No.	Drug (%w/v)	Polymer (5% w/v)	DBP	Chloroform up to (ml)
Control	1.0	EC : PVP 1:1	-	20
C1	1.0	EC : PVP 1:1	10%	20
C2	1.0	EC : PVP 1:1	15%	20
C3	1.0	EC : PVP 1:2	20%	20
C4	1.0	EC : PVP 1:1	25%	20
C5	1.0	EC : PVP 1:1	30%	20
C6	1.0	HPMC : PVP 1:1	20%	20
C7	1.0	EC	20%	20

Table 6: Physical characterizations of the transdermal patches of olmesartan medoxomil

Code no.	Tensile Strength (kg/cm^2)	Folding Endurance	% Elongation	Water vapour permeability ($mg/cm^2/h$)	% moisture loss (%w/w)	Moisture absorption (%w/w)
Control	2.273	>200	33.4	227	0.27	4.16
C1	3.315	>200	76.8	213	0.32	3.78
C2	3.419	>200	84.1	206	0.31	3.69
C3	3.687	>200	93.6	201	0.30	3.53
C4	2.479	>150	37.8	411	0.50	4.86
C5	2.875	>150	46.8	429	0.54	5.11
C6	2.540	>150	58.8	445	0.55	5.40
C7	2.190	>200	60.0	248	0.34	3.80

Table 7: *In-vitro* drug release parameters of various transdermal patches of Olmesartan medoxamil

Code No.	Total drug release in 24 hrs (mg)	Cumulative % Release	Regression coefficient (r^2)	Permeability 1/P.c	Resistsnce Jss(µg/cm^2/h)	Steady state flux ratio (ER)	Enhancement ratio in comparison with Control
Con-trol	8.73 ± 0.05	43.67	0.984	0.031	30.33	0.060	-
C1	10.06 ± 0.03	50.34	0.974	0.033	28.60	0.061	1.15
C2	10.86 ± 0.03	54.32	0.937	0.032	26.62	0.069	1.24
C3	9.60 ± 0.04	48.01	0.951	0.031	26.00	0.072	1.09
C4	13.32 ± 0.08	66.63	0.940	0.042	22.80	0.077	1.52
C5	12.64 ± 0.03	63.23	0.951	0.045	21.13	0.079	1.44
C6	13.98 ± 0.01	57.90	0.933	0.049	19.20	0.085	1.60
C7	14.34 ± 0.02	48.70	0.944	0.045	21.40	0.082	1.64

Table 8: Effect of the accelerated temperature conditions on drug content of transdermal patches of Olmesartan medoxomil

S/No.	Code No.	Drug Content ratio at 4^0c	Drug Content ratio at 25^0c	Drug Content ratio at 40^0c
1.	Control	0.99	0.98	0.96
2.	C1	0.98	0.97	0.94
3.	C2	0.97	0.96	0.94
4.	C3	0.98	0.96	0.94
5.	C4	1.0	0.99	0.97
6.	C5	1.0	0.98	0.98
7.	C6	0.99	0.98	0.97
8.	C7	0.97	0.98	0.96