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Formulation and Evaluation of Olmesartan Medoxomil Transdermal Drug Delivery System

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Abstract

Transdermal patches are cutting-edge drug delivery methods that are essential to the management of many diseases. Due to the avoidance of first pass metabolism the drug molecules are delivered into the systemic circulation at a controlled and predefined pace with the help of TDDS, which also helps to achieve efficient bioavailability. This study's goal was to create matrix-type Olmesartan medoxomil transdermal patches utilizing the solvent evaporation method and various polymer ratios, including HPMC 15 cps, HPMC 5 cps, and Eudragit S 100. Plasticizers like glycerin, propylene glycol, and PEG 200 are used, along with solvents like methanol and chloroform. According to FT-IR studies, pure drugs and excipients are compatible with each other. The generated patches are assessed for their thickness, weight variation, folding endurance, moisture content, drug content, surface pH, and in vitro diffusion studies. Among all the formulations, F6 showed the best characteristic properties and in vitro drug diffusion.

Keywords: Transdermal Drug Delivery System, Olmesartan medoxomil. HPMC 15cps, HPMC 5 cps.

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1. INTRODUCTION

Transdermal Drug Delivery System is a topically administered dosage form containing the Drug and the drug delivery occurs through the skin into the systemic circulation by passive diffusion. TDDS is a self – contained discrete dosage form which when applied on to the intact skin it Delivers the drug molecules into the systemic circulation at a controlled and predetermined Rate [1-3]. TDDS aids in avoiding first pass metabolism and GI irritation of the drugs, increasing bioavailability and lowering harmful side effects, resulting in effective drug delivery of the drug molecules [4-6].

The mechanism of the transdermal drug delivery system is passive diffusion. The three main routes for drug permeation are the trans appendageal route, the transcellular route, and the intercellular route. Depending on the physicochemical properties of the drug molecules, the drug absorption pathway may differ [7, 8].

Olmesartan medoxomil is a prodrug that is hydrolyzed to Olmesartan upon gastrointestinal absorption. Olmesartan medoxomil is a drug which belongs to the class of angiotensin receptor blockers [9-12]. It helps to treat hypertension and also helps to prevent heart attack. Olmesartan acts by blocking the vasoconstrictor action of angiotensin II by selectively blocking the binding of angiotensin II to the AT1 receptors in vascular smooth muscle.

Although Olmesartan medoxomil has an oral bioavailability of 100%, it undergoes extensive first-pass metabolism resulting in reduced bioavailability (26%). Olmesartan medoxomil is an ideal candidate for transdermal patch formulation due to its physicochemical properties such as low melting point, high lipid solubility and biological properties like highly potent, Extensive first pass metabolism and bioavailability. To overcome extensive first pass metabolism and to increase bioavailability Olmesartan medoxomil is formulated as transdermal patches there by resulting in the controlled release of drug into the systemic circulation [13, 14].

2. MATERIALS AND METHODS

Olmesartan medoxomil was obtained as a gift sample from Covalent laboratories Pvt. Ltd, Hyd HPMC 15 cps, HPMC 5 cps was obtained from AR

chemicals, HYd. All other chemicals and reagents utiliaed were of analytical grade.

2.1 UV spectrophotometric method for Olmesartan medoxomil in pH 7.4 phosphate buffer:

Standard stock solution is prepared by taking 10 mg of Olmesartan medoxomil and dissolve in few ml methanol and finally make –up the volume up to 100 ml with pH 7.4 phosphate buffer (100µg/ml). Take 1 ml from the above stock solution (100µg/ml) and make up the Volume up to 10 ml with pH 7.4 phosphate buffer (10µg/ml). Scan the above solution in UV at a wavelength range of 700 to 200 nm to determine the absorption maxima by using as blank. pH 7.4 phosphate buffer.

2.2 Calibration curve of Olmesartan medoxomil in pH 7.4 phosphate buffer:

Take 10 mg of Olmesartan medoxomil and dissolve the drug in few ml of methanol and make-up the volume up to 100 ml with pH 7.4 phosphate buffer (100µg/ml). Serial dilutions of 5–25µg / ml are prepared and scanned in UV by using as blank. pH 7.4 phosphate buffer

2.3 Drug excipient compatibility Studies by FT- IR:

Drug excipient compatibility Studies can be determined by FT-IR by analyzing with pure drug and physical mixture of both drug and excipients.

2.4 Method of preparation of Olmesartan medoxomil transdermal patches:

Matrix type transdermal patches containing OLMESARTAN MEDOXOLOL were prepared by solvent evaporation technique, using different ratios of HPMC 5cps, HPMC15cps and Eudragit S100 were weighted in requisite ratios for patch preparation and they are allowed for swelling for about 6hrs in a solvent mixture and plasticizer PEG 200 or Propylene glycol and glycerin were added.

Then the drug solution was added to the polymeric solution, casted on to petri plate, and it is allowed for air drying overnight followed by vacuum drying for 8-10hrs.

Table-1: Formulation table of Olmesartan medoxomil transdermal patches

Ingredients	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12
Drug (mg)	20	20	20	20	20	20	20	20	20	20	20	20
HPMC 15 cps (mg)	26.3	26.3	-	-	13.15	13.15	-	13.15	6.57	6.57	13.15	13.15
Eudragit S 100(mg)	-	-	26.3	-	13.15	-	13.15	6.57	13.15	6.57	-	13.15
HPMC 5cps(mg)	-	-	-	26.3	-	13.15	13.15	6.57	6.57	13.15	13.15	-
Methanol (ml)	0.05	0.05	0.05	0.05	0.05	0.05	0.05	0.05	0.05	0.05	0.05	0.05
Chloroform (ml)	-	0.05	0.05	0.05	0.05	0.05	0.05	0.05	0.05	0.05	0.05	0.05
Water (ml)	0.05	-	-	-	-	-	-	-	-	-	-	-
PEG 200 (ml)	0.05	-	0.05	0.05	0.05	0.05	0.05	0.05	0.05	0.05	-	-
Propylene glycol (ml)	-	0.05	-	-	-	-	-	-	-	-	0.05	0.05
Glycerin (ml)	0.05	0.05	0.05	0.05	0.05	0.05	0.05	0.05	0.05	0.05	0.05	0.05

2.5 Evaluation tests [15-22]:

I. Weight variation:

Weight variation was determined by cutting the transdermal patch into 2 cm square and the weight of 3 patches was determined and the average weight was calculated.

II. Thickness:

Thickness of 3 patches were determined by using Vernier calipers. Thickness was measured at three different points on the patch and the average readings were recorded.

III. Folding endurance:

A patch of 2cm square was cut evenly and repeatedly folded at the same place till it brakes. The value of the folding endurance is determined by the number of times the film was folded at the same location without breaking.

IV. Surface pH:

Films of 2 cm square are placed in 0.5ml of double distilled water in a glass tube for about 1 hour and pH of the film was calculated using pH meter.

V. Drug content:

Films of 2cm square are placed in a mixture of 20ml Methanol and 80ml pH 7.4 phosphate buffer in 100ml volumetric flask and stirred by using magnetic stirrer for 24 hours. Drug solution was scanned in UV spectroscopy and drug content was calculated.

VI. Percentage of moisture content:

Films of 2 cm square are weighed individually and stored in a desiccator for about 24hrs at room temperature and moisture content was calculated using formula:

Moisture content = initial weight – final weight / final wweight×100

VII. *In vitro* drug diffusion studies:

In vitro drug release diffusion studies is performed by using Franz diffusion cell. It consists of receptor compartment of 22.5ml capacity and it also contains donor compartment. The receptor compartment was filled with pH 7.4 phosphate buffer cellophane membrane was Placed between the donor and receptor compartment. The prepared transdermal

patch was placed on cellophane membrane. The whole assembly was fixed on a magnetic stirrer and continuously stirred at 50rpm.The temperature was maintained at 32 ± 0.5 ºC. The samples were withdrawn at different time intervals and analyzed in UV spectroscopy. The receptor chamber was replenished with an equal amount of pH 7.4 phosphate buffer to Maintain sink conditions. A graph was plotted between cumulative percentage of drug permeation per square centimeter of patches against time.

3. RESULTS AND DISCUSSION

3.1 UV spectrum of Olmesartan medoxomil in pH 7.4 phosphate buffer:

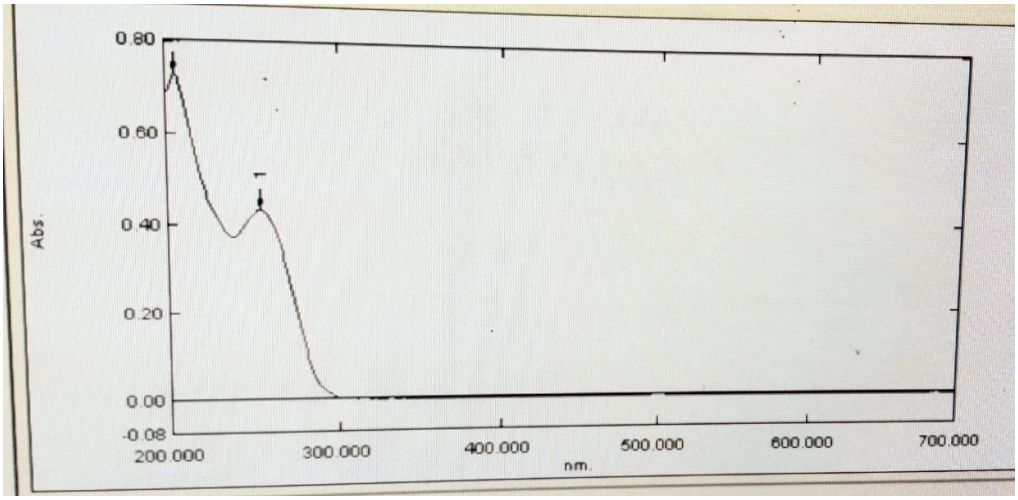

Fig-1: UV spectrum of Olmesartan medoxomil in pH 7.4 phosphate buffer maximum absorption was found at 254nm

3.2 Calibration curve of Olmesartan medoxomil in pH 7.4 phosphate buffer:

Table-2: Calibration curve of Olmesartan medoxomil in pH 7.4 phosphate buffer

Concentration(ppm)	Absorbance
0	0
5	0.165
10	0.301
15	0.456
20	0.667
25	0.827

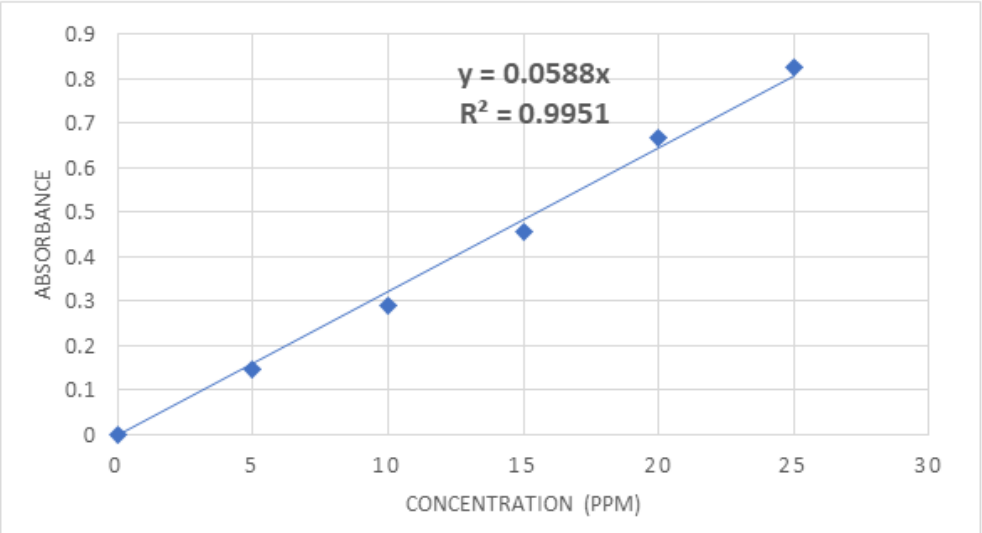

Fig-2: Calibration curve of Olmesartan medoxomil in pH 7.4 phosphate buffer graph was found to be linear and R^2 was found to be 0.9951

3.3 FTIR spectrum of Olmesartan medoxomil:

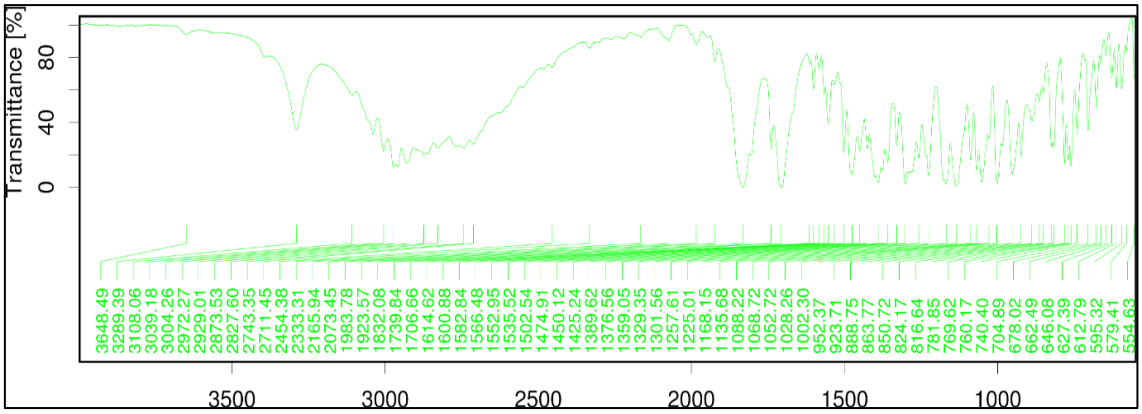

Fig 3: FTIR spectrum of Olmesartan medoxomil

3.4 FTIR spectrum of Formulation F6:

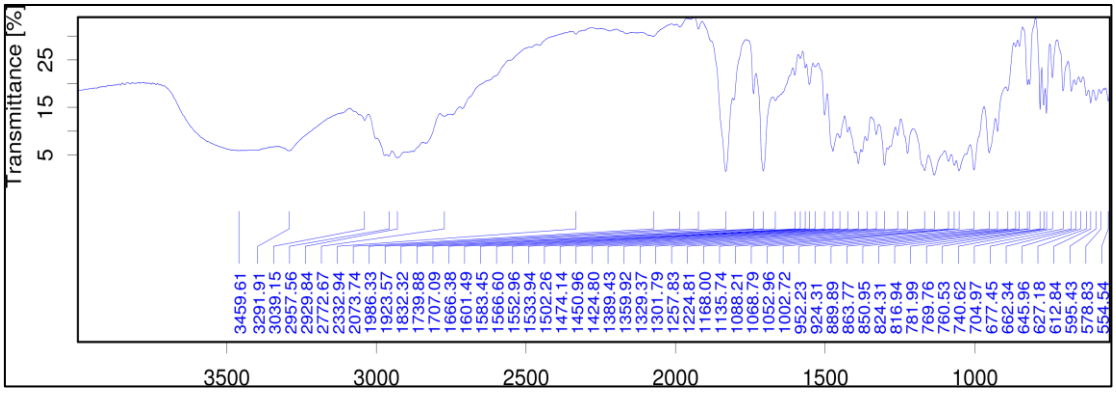

Fig-4: FTIR spectrum of Formulation F6

Both the pure drug and excipients are compatible with each other.

3.5 Evaluation tests:

Table-3: Evaluation tests of Olmesartan medoxomil transdermal patches

Formulation	Weight variation ± SD n=3	Thickness ± SD n=3	Folding endurance± SD n=3	Surface pH ± SD n=3	Drug content ±SD n=3	% moisture content ± SD n=3
F1	1.32±0.86	0.27±0.03	280± 2	6.01±0.05	97.49±0.03	2.21±0.07
F2	11.6±0.024	0.26±0.07	290± 3	5.98±0.02	90.12±0.001	1.36±0.01
F3	2.20±0.002	0.28±0.09	289± 3	5.92±0.07	88.23± 0.02	1.98±0.06
F4	2.48±0.024	0.23±0.08	280± 2	6.03±0.01	75.54±0.011	1.30±0.012
F5	6.35±0.002	0.24±0.26	300± 4	6.05±0.10	82.56± 0.09	2.36± 0.14
F6	0.07± 0.05	0.22±0.02	350± 3	6.10±0.120	99.23± 0.02	1.03± 0.07
F7	2.8± 0.04	0.23±0.41	310± 3	6.03± 0.15	91.12± 0.08	1.52± 0.26
F8	4.63±0.081	0.25±0.80	290± 2	5.89± 0.03	89.54± 0.05	1.42± 0.07
F9	5.52± 0.86	0.27±0.09	280± 4	5.86± 0.01	86.67± 0.06	1.98± 0.01
F10	2.6± 0.05	0.28±0.12	294± 2	5.96± 0.05	72.34± 0.09	2.21± 0.06
F11	6.95± 0.03	0.23±0.11	326± 2	5.85± 0.08	82.79± 0.03	2.45± 0.15
F12	3.74± 0.02	0.26±0.30	277± 3	5.92± 0.02	83.21± 0.06	1.49± 0.62

Weight variation was measured for all the formulations and weight variation was found to be in the range of 0.07 to 11.6 ± 0.05. values of weight variation are shown in the table-3.

Thickness was measured for all the formulations and thickness was found to be in the range

of 0.22 to 0.28± 0.02. values of thickness are shown in the Table-3.

Folding endurance was measured for all the formulations and Folding endurance was found to be in the range of 277 to 350 ± 3. values of Folding endurance are shown in the Table-3.

Surface pH was measured for all the formulations and surface pH was found to be in the range of 5.86 to 6.10± 0.05. values of surface pH are shown in the Table-3.

Drug content was measured for all the formulations and drug content was found to be in the range of 72.34 to 99.23± 0.06. values of drug content are shown in the Table-3.

% moisture content was measured for all the formulations and % moisture content was found to be in the range of 1.03 to 2.45± 0.07. values of % moisture content is shown in the Table-3.

3.6 *In vitro* drug diffusion studies:

Table-4: *In vitro* drug diffusion studies of F1 to F6

Time(hrs)	F1	F2	F3	F4	F5	F6
0	0	0	0	0	0	0
0.25	5.12±4.98	4.32±1.03	3.89±1.64	4.02±1.74	3.54±1.56	2.05±3.46
0.5	10.56±5.78	9.65±4.02	7.48±1.74	8.71±4.54	7.02±2.24	3.67±4.54
1	22.13±4.03	21.24±4.04	15.84±3.46	17.26±2.64	14.51±3.52	5.67±3.42
2	43.15±5.97	43.56±3.01	31.45±2.84	35.42±3.51	29.57±2.34	13.02±5.36
4	74.65±5.89	63.61±2.06	58.15±4.76	56.26±2.12	48.62±4.12	23.56±4.53
6	92.45±5.79	76.35±5.03	67.21±4.67	67.52±2.34	59.47±2.31	34.03±5.16
8	-	89.94±2.02	83.23±5.35	79.89±4.56	68.97±1.16	44.25±4.43
12	-	-	93.14±3.72	89.98±1.31	80.47±5.29	62.54±5.61
16	-	-	-	-	91.62±4.34	80.12±5.37
24	-	-	-	-	-	98.24±5.14

Table 5: *In vitro* drug diffusion studies of F7 to F12

Time(hrs)	F7	F8	F9	F10	F11	F12
0	0	0	0	0	0	0
0.25	5.11±1.35	3.54±1.74	4.15±126	3.98±1.43	3.26±1.86	4.65±1.54
0.5	10.23±1.42	8.04±1.64	9.41±3.34	8.45±3.62	7.89±0.43	8.99±1.16
1	21.03±2.61	16.47±3.52	19.35±2.62	17.68±2.51	15.48±256	18.45±2.48
2	43.02±2.54	33.54±1.25	42.15±1.53	36.78±2.34	32.05±3.14	37.16±2.37
4	1.02±4.31	58.43±4.37	64.36±4.42	69.76±5.26	56.22±2.53	59.78±3.61
6	90.32±3.27	66.27±2.49	77.54±1.31	80.64±1.74	67.54±3.26	69.23±1.53
8	-	79.56±2.57	90.48±4.14	92.43±4.61	76.54±2.53	81.24±5.25
12	-	92.14±5.63	-	-	83.12±4.47	87.45±4.63
16	-	-	-	-	91.14±5.67	-
24	-	-	-	-	-	-

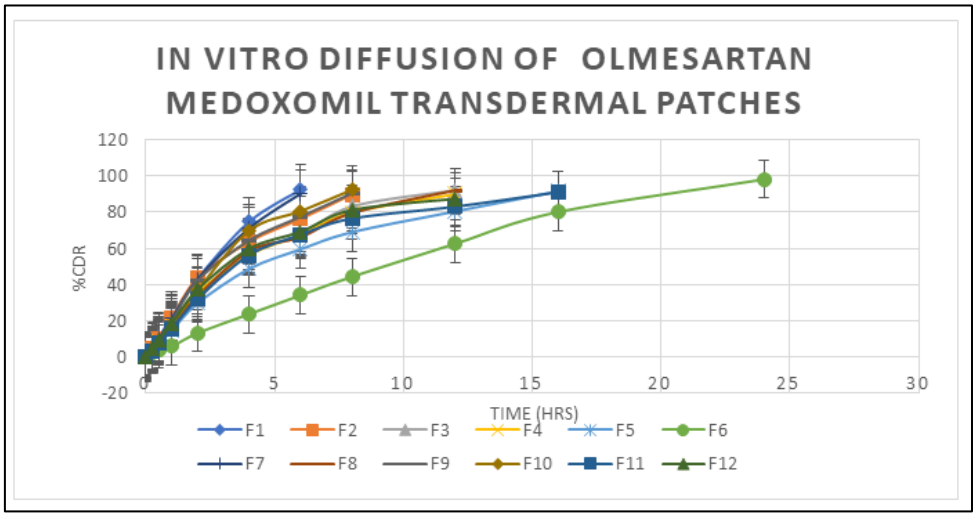

Fig 5: In vitro drug diffusion studies of F1to F12

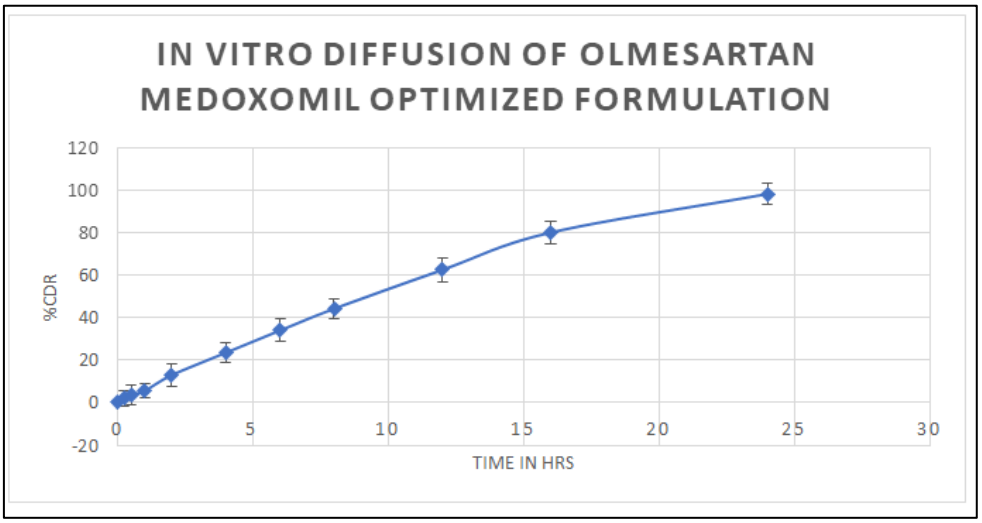

Fig 6: In vitro diffusion of Olmesartan Medoxomil (F6)

The data obtained from the in vitro drug diffusion studies is shown in the Table 4 and 5. In vitro drug diffusion studies are performed for 24hrs. All the prepared patches have shown controlled release at a range of 6 to 16 hrs except F6 (24hrs). In vitro drug diffusion studies are carried out using pH 7.4 phosphate buffer at 254nm. Among them F6 shows highest drug release at the end of 24th hour.so, F6 formulation chosen as the best formulation as it releases the drug at a slow rate for longer duration of time.

Fig-7: Best formulation F6

Fig 8: Zero order release kinetics for best formulation (F6)

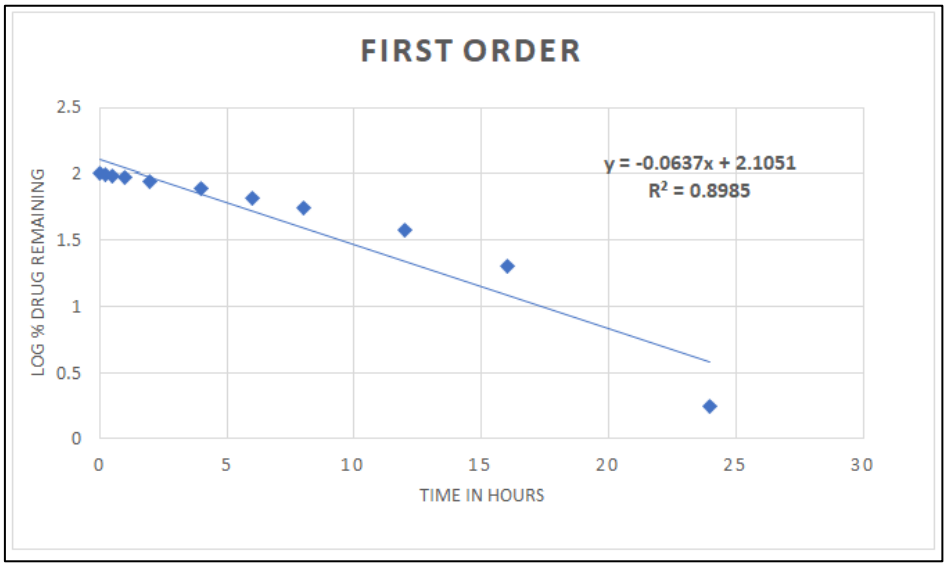

Fig 9: First order release kinetics for best formulation (F6)

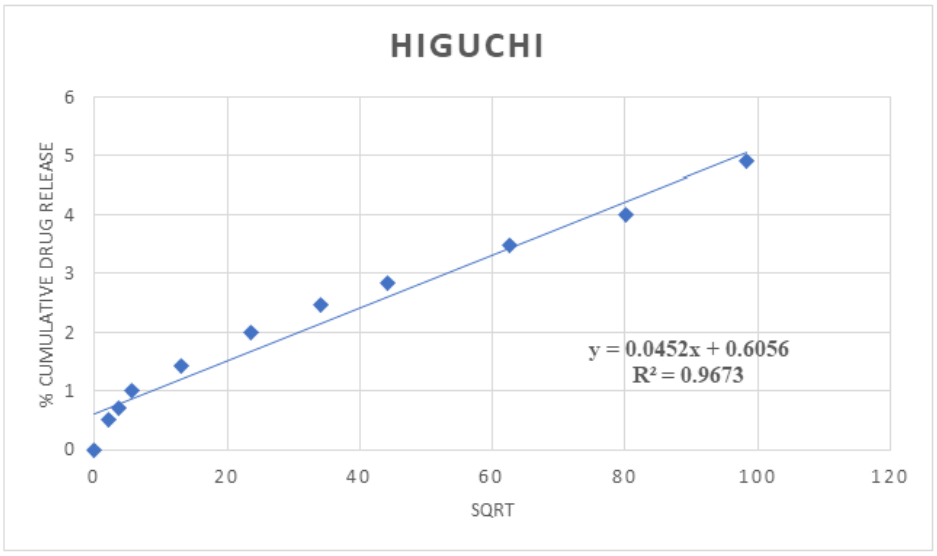

Fig 10: Higuchi release kinetics for best formulation (F6)

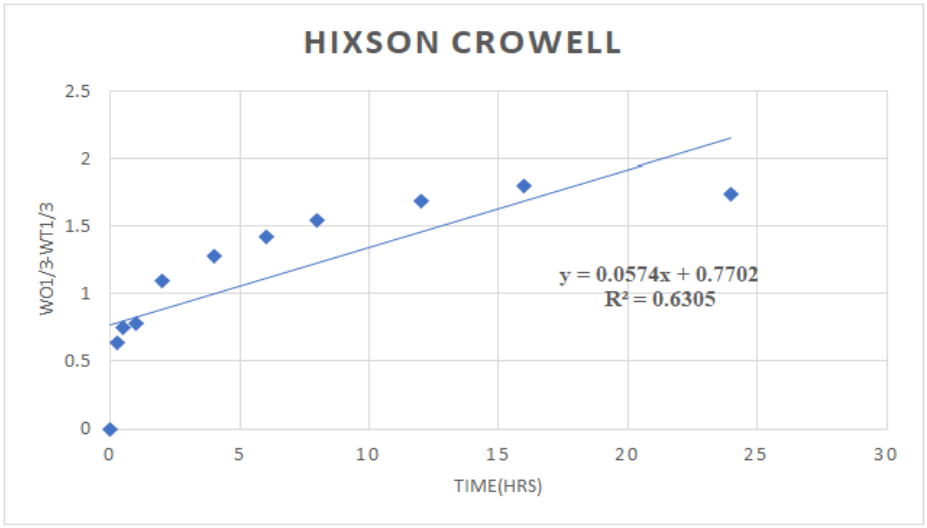

Fig 11: Hixon-Crowell release kinetics for best formulation (F6)

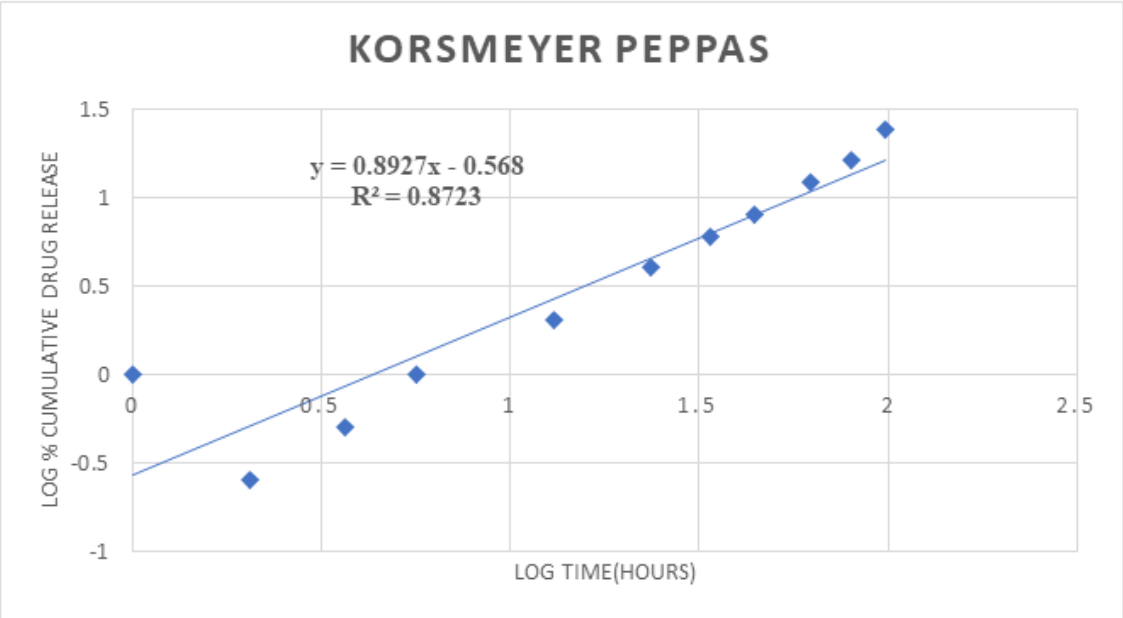

Fig 12: Korsemeyer-Peppas release kinetics for best formulation (F6)

Follows zero order kinetics with diffusion type of drug release.

4. CONCLUSION

Among all the formulations prepared F6 shows best results. All the physicochemical properties of F6 were found to be satisfactory. The patch exhibit-controlled release over 24hrs.The results of the study shows that Olmesartan medoxomil can be delivered by transdermal patches. The result of the current investigation suggests that the transdermal patch containing Olmesartan medoxomil may have great promising for effective doses into systemic circulation.

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