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Formulation and Evaluation of Transdermal Patches of Anti-Hypertensive Drug

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Abstract:
The aim of the study was to develop suitable transdermal drug delivery system of Losartan potassium with a view to prevent its first pass hepatic metabolism, to achieve a controlled drug release and improved bioavailability. The transdermal patches of losartan potassium were prepared by solvent casting technique. A combination of Polyvinyl Pyrrolidone (PVP-K30) and Polyvinyl Alcohol (PVA) with Urea, and Poly Ethylene Glycol (PEG200) as plasticizer was used to design transdermal patches. Seven formulations (F1, F2, F3, F4, F5, F6, and F7) were developed, with different proportions of polyvinyl pyrrolidone and polyvinyl alcohol. Patches prepared were evaluated by various parameters like thickness, folding endurance, swelling index, moisture content, moisture uptake, flatness, weight uniformity, watervapour transmission (WVT) rate, tensile strength, bursting strength, and in-vitro drug release study. Compatibility study using differential scanning calorimetry and FT-IR. In different formulation on the basis of present study formulation F7 show satisfactory drug release pattern.

Keywords: *Transdermal drug delivery system, losartan potassium, Polyvinyl Pyrrolidone (PVPK30), Polyvinyl Alcohol (PVA), Urea, Poly Ethylene Glycol (PEG200).*

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I. Introduction

Transdermal patch (Skin patch) uses a special membrane to control the rate at which the liquid drug contained in the reservoir within the patch can pass through the skin and in to the blood stream. Some drugs must be combined with substances, such as alcohol, that increase their ability to penetrate the skin in order to be used in a skin patch. Drugs administered through skin patches include scopolamine (for motion sickness), nicotine (for quitting smoking), estrogen (form Menopause and to prevent osteoporosis after menopause), nitroglycerin (for angina),and lidocaine to relieve the pain of shingles (herpes zoster). Molecules of insulin and many other substances are too large to pass through the skin.1Patches applied to the skin eliminate the need for vascular access by syringe or the use of pumps. Transdermal patches were developed in the 1970s and the first was approved by the FDA in 1979 for the treatment of motion sickness .It was a three-day patch that delivered scopolamine. In1981, patches for nitroglycerin were approved, and today there exist a number of patches for drugs such as clonidine, fentanyl, lidocaine, nicotine, nitroglycerin, estradiol, oxybutynin, scopolamine, and testosterone. There are also combination patches for contraception, as well as hormone replacement. Depending on the drug, the patches generally last from one to seven days.[2]

The major advantages provided by transdermal drug delivery include the following: improved bioavailability, more uniform plasma levels, longer duration of action resulting in a reduction in dosing frequency, reduced side effects and improved therapy due to maintenance of plasma levels up to the end of the dosing interval compared to a decline in plasma levels with conventional oral dosage forms. Transdermal patches have been useful in developing new application s for existing therapeutics and for reducing first-pass drug-degradation effects. Patches can also reduce side effects; for example, estradiol patches are used by more than a million patients annually and, in contrast to oral formulations, do not cause liver damage. Of two major sub-categories therapeutic and cosmetic), aroma patches weight loss patches, and Non-medicated patch markets include thermal and cold patches, nutrient patches, and skin care patches (a category that consists patches that measure sunlightexposure.[3,4]

II. Material And Methods

Losartan potassium gift sample obtained from micro laboratories, and other excipients like PVA purchased from Ebonics pharm Pvt. Ltd Mumbai, PVPK30 Purchased from SD fine Chemicals Ltd Mumbai, and other excipients obtained from local vendors

Methodology:-

Preparation of transdermal patch 5

Transdermal patches containing Losartan potassium were casted on by solvent evaporation technique. The drug matrix was prepared by dissolving PVPK30 in distilled water and PVA was also dissolved in warmed distilled water. And Urea added to mixture of solution in a PVA and PVPK30. Polyethylene glycol (200) was used as a plasticizer. The antihypertensive drug 100 mg of Losartan potassium was added and the homogenous dispersion was produced by slow stirring with a magnetic stirrer. After complete drying of patches were cut into small pieces each of 1 square centimeter and stored between sheets of wax paper in desiccators.

Table1: Formulation of losartan potassium transdermal patches:

SI.No	Ingredients	F1 (1:2)	F2 (1:3)	F3 (1:4)	F4 (1:4)	F5 (1:2:3)	F6 (1:2:4)	F7 (1:2:3)
1	Losartan Potassium (mg)	100	100	100	100	100	100	100
2	PVA (mg)	200	300	4000	400	200	200	200
3	PVPK30 (mg)	-	-	-	-	300	400	300
4	UREA (mg)	-	-	-	1%	-	-	1%
5	PEG200 (mg)	3%	3%	3%	3%	3%	3%	3%
6	Water (ml)	10ml	10ml	10ml	10ml	10ml	10ml	10ml

Evaluation of transdermal patches:

The transdermal membranes prepared were evaluated for the following parameters:

Thickness
Folding endurance
Swelling index
Drug content
Moisture content
Moisture uptake
Flatness
Weight uniformity
Water vapor transmission (wvt) study
Tensile strength test
Bursting strength
In-vitro permeation study
Stability studies

Thickness[6]

Thickness of all the membranes were measured at three different points on each membrane Average of five readings was taken, using screw gauge.

Folding endurance[7]

A modified USP tablet disintegrating tester was used to determining the folding endurance of the membrane. It consisted of fixed and movable jaws that could be moved up and down at the rate of
30 strokes per minute. The distance between the 2 jaws at their farthest and closest were 6 centimeter and 0.5 centimeter respectively. The membrane (6cm length) was clamped between the jaws in such a way that the jaws were at their closest, the membrane beat across its middle and when at the membrane was in a Stretched condition. Thus for every stroke of the movable jaw the membrane went through One cycle of bending and stretching. The folding endurance is expressed as the number of Strokes required to either break or develop visible cracks on the membrane. The test was conducted for 20 min equating 600 strokes. The locally modified folding endurance tester.

Swelling index

The polymeric membrane cut into $1cm^2$ were weighed accurately and allowed to swell on a agar gel plate contain 2% w/v. Individual membranes were weighed periodically until they showed a constant weight.

$$\text{Swelling index} = \frac{\text{wet weight-initial weight}}{\text{Wet weight}} \times 100$$

Drug content

Patches of specified area were dissolved in 7. 2pH Phosphate buffer and the volume were made up with 7.2pH phosphate buffer. Blank was prepared using drug free patch treated similarly. The solution was filtered through membrane, diluted with a suitably and absorbance were measured at 205 nm double beam UV–Visible spectrophotometer (ShimadzuUV-1700)

Percentage of moisture content

The membrane of size 1 cm^2 were weighed individually and stored in desiccators consists off used calcium chloride at room temperature for 24 h. Individual membranes were weighed repeatedly until they showed a constant weight. The percentage of moisture content was calculated as the difference between initial and final weight with respect to

$$\% \text{ moisture content} = \frac{\text{Initialweight-Finalweight}}{\text{Final weight}} \times 100$$

Percentage of moisture uptake

A weighed membrane of size 1 cm^2 stored in desiccators at room temperature for 24 hrs. Was taken out and exposed to 84% relative humidity (a saturated solution of potassium Chloride) in desiccators until a constant weight for the membrane was obtained. The Percentage of moisture uptake was calculated as the difference between final and initial Weight with respect to initial weight

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 center 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 to100percent flatness.

% constriction = I1–I2X100I2=Final length of each strip I 1 =Initial length of each strip

Weight uniformity

Ten prepared films are randomly selected and dried at 60^0 C for 4 hrs. Before testing. These films are weighed individually on digital balance. The average weight was calculated and their individual weights were compared with average weight.

Water vapor transmission (WVT) study [8]

The membrane 1×1 cm^2 was fixed over the brim of a glass vial, consists of 2 g of fused calcium chloride as desiccant. The vial was weighed and kept in desiccator contain saturated solution of potassium chloride to provide 84% relative humidity. The vial was taken out and weighed at every 24 h intervals for a period of 7 days. The flux i.e. the amount of water vapors transmitted through 1centimeter^{2}per 24h and permeability coefficient was calculated using the formula.

$$P = \frac{\text{SLOPE}}{24 \text{`P'}}$$

Where=Permeability Coefficient.

'P'=Vapor Pressure of Saturated Solution of Potassium Chloride

Tensilestrengthandextension[9]

Tensile strength of the films was determined by using house field universal testing machine. The sensitivity of the machine was 1 mg – 500 mg. It consists of two load cell jaws. The upper one is movable and lower one was fixed. The films of specific size (4x1cms) was fixed between these grips and upper jaw was moved at a speed of 100 mm/min. applying force gradually till the films break. The tensile strength of the films was taken directly from the dialed reading in kilogram and extension off l min mm.

Bursting strength

A test for measuring the resistance of a film to bursting and reported in kilo-Pascal or Pounds per square inch or kg/cm2. The burst strength of all the patches was evaluated by using standard bursting strength tester.

***Invitro*skinpermeationstudy[10, 11]**

The *in vitro* skin permeation experiments were conducted in a modified Franz diffusion Cell (receptor compartment capacity: 16 ml; surface area: 1.5 cm2). The diffusion cell consists of two compartments; the upper compartment i.e. the donor compartment which contains the transdermal system with the dialysis membrane; the bottom part contains the Receptor solution, the water jacket for temperature control and the sampling port. The Permeation study was carried out across the dialysis membrane-110. The receiver Compartment was filled with 16 ml of phosphate buffer pH7.2. The donor compartment was then placed in position such that the surface of the membrane just touches the

receptor Fluid surface. The whole assembly was placed on a magnetic stirrer, and the solution in the Receptor compartment was constantly and continuously stirred at 50 rpm; the temperature of whole assembly was maintained at 37 ± 0.5ºc by circulating hot water inside the water jacket. The samples were withdrawn at different time intervals up to 24 h and replenished with an equal volume of buffer solution at each time interval. The absorbance of withdrawn samples was measured at 205nmusingU.Vspectrophotometer.

Stability studies[12]

Accelerated stability study: The optimized patches were subjected to stability studies to evaluate any change in the performance when exposed to accelerated conditions of environment during storage, handling transport and use. The patches were packed in the aluminum foil and kept at 40± 2oc and 75 ±5% RH as per ICH guidelines. (ICH Q1A [R2] Stability testing new drugs substances and products).

III. Result

Standard curve for losartan potassium:

The absorbance was measured in a UV-spectrophotometer at 205 nm against phosphate buffer pH 7.2 as blank. The absorbance so obtained was tabulated as in Table5.1 and calibration curve was plotted and shown in Figure 1

Figure1: Standard curve of Losartan potassium drug

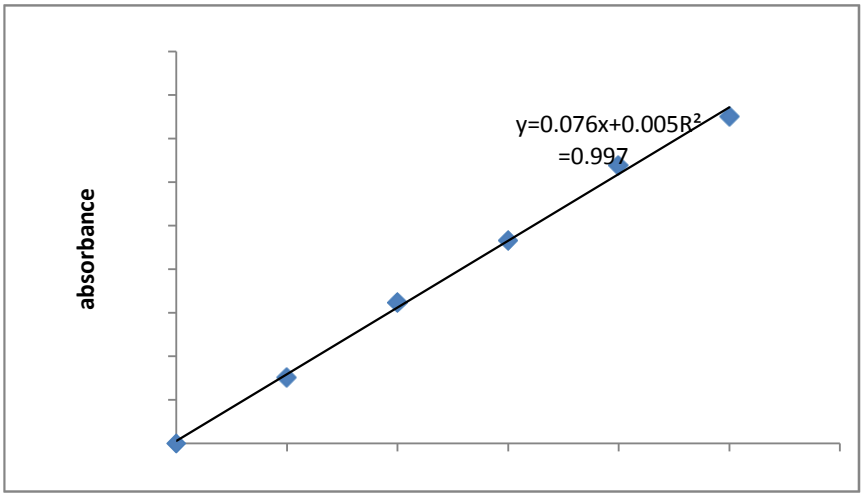


Table 2: The wave numbers representing principal peak of the FT-IR spectra of drug and polymer

	Losartan potassium	**PVA+DRUG**	**PVP K30+DRUG**	**UREA+DRUG**	**COMBINATION**
Functional group OH	3175.46	3242.22	3183.65	3320.55	3197.58
CH stretching (Aromatic)	3033.34	2925.79	3135.87	3208.12	2942.14
CH stretching (Aliphatic)	2925.87	2858.74	2926.27	2926.22	2924.15
C=O	1575.75	1575.42	1575.07	1593.08	1597.08
C=C	1500.21	1500.20	1500.07	1500.61	1500.59
Al-CH-bend	1458.25	1458.85	1458.78	1453.61	1434.52
Ar-CH Inplane bending	1071.55	1101.00	1000.93	1098.53	1099.41
Ar-CH Outplane bending	933.91	997.95	995.63	998.28	999.99
C-O-C Ether linkage	1106.40	1250.50	1253.51	1249.0	1287.60

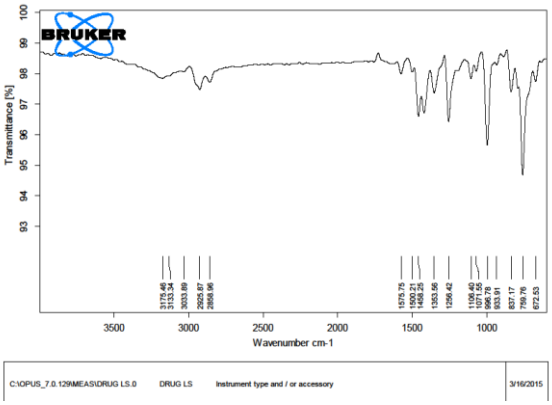


Figure 2: FT-IR spectra of Losartan potassium Drug

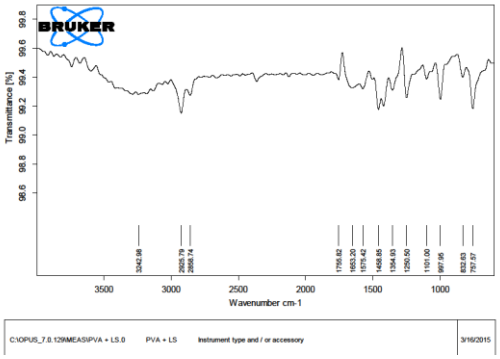


Figure 3: FT-IR spectra of Losartan potassium Drug+PVA

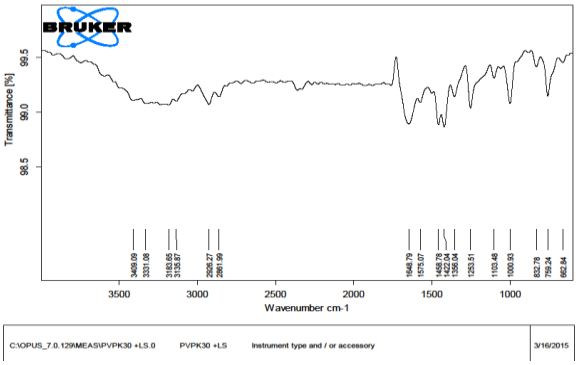


Figure 4: FT-IR spectra of Losartan potassium Drug+PVP K30

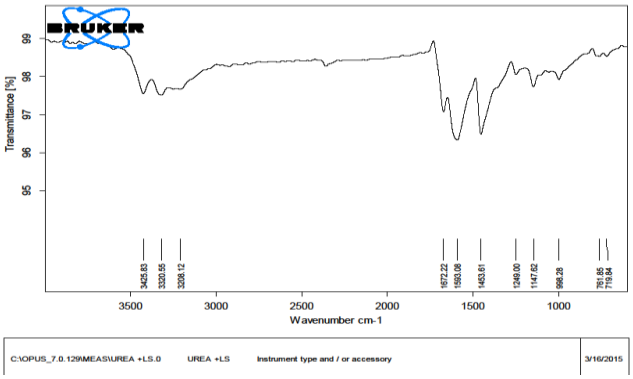


Figure 5: FT-IR spectra of Losartan potassium Drug+Urea

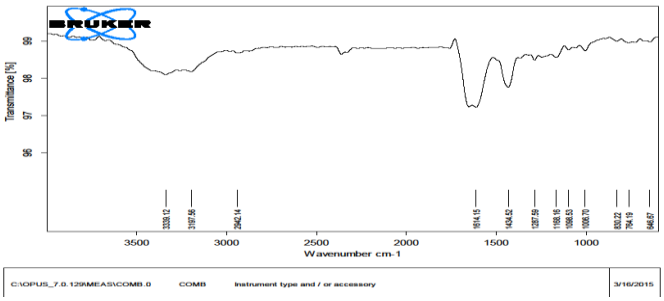


Figure 6: FT-IR spectra of combination

Compatibility study using differential scanning calorimetry (DSC)

The DSC analysis of losartan potassium alone showed a sharp endothermic peak at 273.44 °C corresponding to its melting point, it indicate the drug sample was pure. The DSC analysis of losartan potassium with PVAand PVP K30. Demonstrated negligible change in the melting point of losartan potassium (275.85°C), which indicated that the polymers do not interact with the drug. The DSC thermogram of Losartan potassium and losartan potassium with PVA and PVP K30 are shown in Figure 7 and Figure 8

Table 3: Characteristic peaks for DSC sample

Sl.No	Sample combination	Peak
1	Losartan potassium	273.44^0 C
2	Losartan potassium + pva + pvp k30	275.85^0C

Figure 7: DSC thermogram of losartan potassium

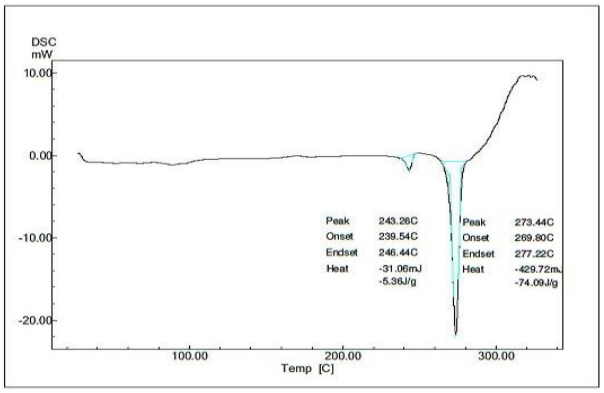
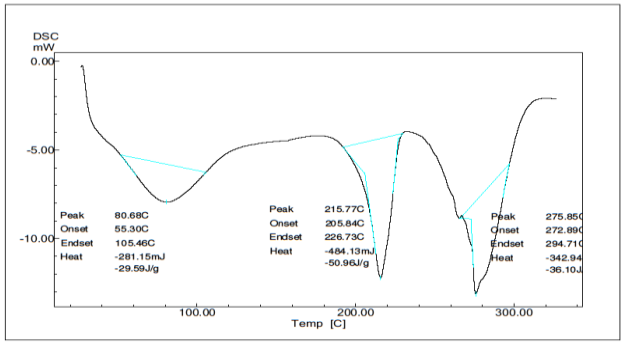


Figure 8: DSC thermogram of losartan potassium+PVA +PVP K30



EVALUATION OF TRANSDERMAL FILMS

Thickness

The thickness of each patch was measured at the different sites using screw gauge and the average thickness was calculated. Percentage deviation from mean thickness was determined are given in table [5]

Table 4: Thickness of different formulations

Sl. No	Formulation Code	Thickness (µm)
1	F1	0.260
2	F2	0.285
3	F3	0.324
4	F4	0.340
5	F5	0.456
6	F6	0.485
7	F7	0.460

Mean (n=3)

Drug Content

Patches of specified area were dissolved in 7. 2pH Phosphate buffer and the volume were made up with 7.2pH phosphate buffer. Blank was prepared using drug free patch treated similarly. The solution was filtered through membrane, diluted with a suitably and absorbance were measured at 205 nanometer in a double beam UV – Vis spectrophotometer (Shimadzu UV-1700) .

Table 5: Drug Content of different formulations

Sl. No	Formulation Code	Drug Content%
1	F1	95.16
2	F2	96.08
3	F3	96.30
4	F4	97.08
5	F5	97.02
6	F6	95.87
7	F7	98.06

Mean (n=3)

Folding endurance

The folding endurance was measured manually for the prepared films strip of the films. 2 x 2 cm 2 was cut evenly and repeatedly folded at the same place till it broke. The number of films could be folded at the same place without breaking give the exact value of the folding endurance.

The folding endurance of all the membranes were measured in triplicate, according to procedure given in section and the results are shown in Table 6

Table 6: Folding of different formulations

Sl. No	Formulation Code	Folding Endurance
1	F1	66
2	F2	73
3	F3	78
4	F4	91
5	F5	96
6	F6	94
7	F7	99

Mean (n=3)

Swelling index

Swelling index was determined by allowing patches to swell in an agar gel plate which contain 2% w/v agar. The percentage swelling index was calculated as the difference between wet weight and initial weight with respect to wet weight. The results of the swelling index studies for different formulations are shown in Table 7

Table 7: Swelling index of different formulations

Sl. No	Formulation Code	Swelling index
1	F1	45.02
2	F2	57.08
3	F3	65.04
4	F4	70.12
5	F5	82.18
6	F6	90.13
7	F7	98.10

Mean (n=3)

Percentage moisture content

The moisture content was determined by keeping membranes in a desiccators contained fused calcium chloride. The percentage moisture content was calculated as the difference between initial and final weight with respect to final weight. The results of the moisture content studies for different membranes are shown.

Percentage moisture uptake

The percentage moisture uptake was calculated as the difference between final and initial weight with respect to initial weight. The results of moisture uptake studies for different membranes are shown.

Table 8: Percentage moisture content and percentage moisture uptake of different Formulations

Sl. No	Formulation Code	% Moisture Content (%)	% Moisture Uptake (%)
1	F1	2.89	1.21
2	F2	2.38	1.11
3	F3	1.94	1.06
4	F4	2.79	1.50
5	F5	2.10	1.51
6	F6	2.18	1.29
7	F7	2.30	1.38

Mean (n=3)

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 center 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

. % constriction = I1 – I2 X 100 I2 = Final length of each strip I1 = Initial length of each strip

Table 9: Flatness of different formulations

Sl. No	Formulation Code	Flatness
1	F1	99.9
2	F2	100
3	F3	100
4	F4	99.8
5	F5	100
6	F6	99.9
7	F7	100

Mean (n=3)

Weight uniformity

Ten prepared films are randomly selected and dried at 60^0 C for 4 hrs. Before testing. These films are weighed individually on digital balance. The average weight was calculated and their individual weights were compared with average weight.

Table 10: Weight uniformity of different formulations

Sl. No	Formulation Code	Weight uniformity
1	F1	18
2	F2	23
3	F3	25
4	F4	30
5	F5	28
6	F6	29
7	F7	32

Mean (n=3)

Water Vapour transmission study

For this study, vials of equal diameters were used as transmission cells. These cells were washed thoroughly and dried in oven. About 1 g of calcium chloride was taken in the cell and the polymeric films measuring 1×1 cm^2 areas were fixed over the brim with the help of an adhesive. The cell's initial weight was recorded. These were kept in desiccators

Containing saturated solution of potassium chloride (about 200 ml). The humidity inside the desiccator was measured by hygrometer, and it was found to be in between 80-90% RH. The cells were taken out and weighed. Then water vapour transmission rate was calculated.

Water vapour transmission rate (W.V.T) = WL/S where W = Water vapour transmission in g and L = Thickness of the film in cm and S = Exposed surface area

And the results are shown the table 11

Table 11: Water vapor transmission study membranes.

Sl. No	Formulation Code	Water vapour transmission rate (W.V.T)
1	F1	0.3148
2	F2	0.3260
3	F3	0.3483
4	F4	0.3538
5	F5	0.3615
6	F6	0.3778
7	F7	0.4005

Mean (n=3)

Tensile strength of film

Tensile strength of the films was determined by using house field universal testing machine. The tensile strength of the films was taken directly from the dialed reading in kilogram of film in mm.

Table 12: Tensile strength of different membranes**.**

Sl. No	Formulation Code	Tensile strength
1	F1	0.9158
2	F2	0.8311
3	F3	0.6584
4	F4	0.6150
5	F5	0.5950
6	F6	0.5420
7	F7	0.3240

Mean (n=3)

Bursting strength of film

The bursting strength of all the films were evaluated by using standard bursting strength tester and the average bursting strength of all films was given in Table 13

Table 13: Bursting strength of different membranes.

Sl. No	Formulation Code	Bursting strength (Kg/cm2)
1	F1	4.466
2	F2	4.166
3	F3	3.872
4	F4	3.538
5	F5	3.366
6	F6	3.312
7	F7	3.025

Mean (n=3)

***In vitro* permeation Studies**

The *in vitro* permeation studies are predictive of *in vivo* performance of a drug. These studies were performed for different membranes across dialysis membrane no 110 using phosphate buffer, pH 7.2 as an *in vitro* study fluid in the receptor compartment of a modified Franz diffusion cell.

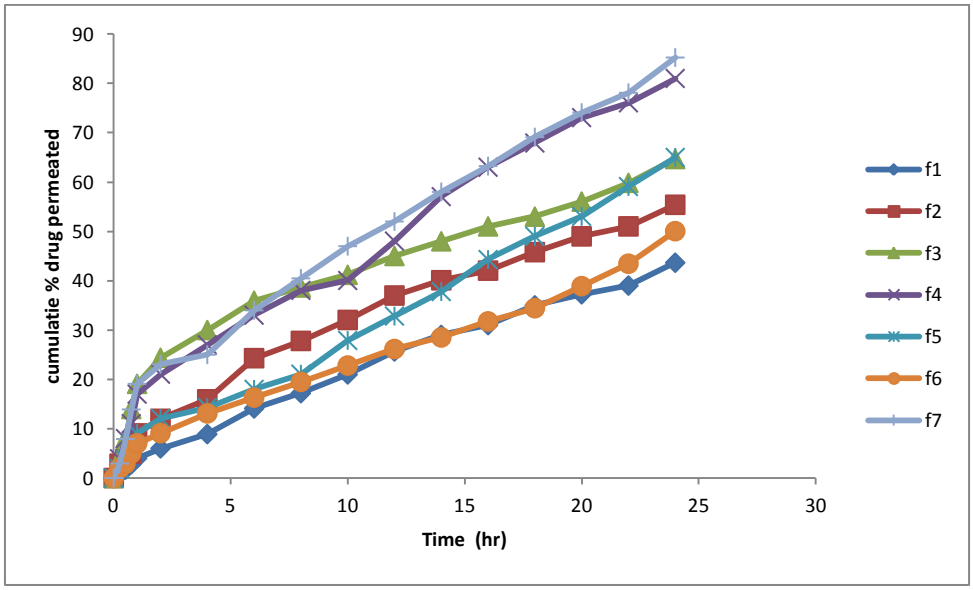


Figure 9: In-vitro Permeation of membranes F1 to F7

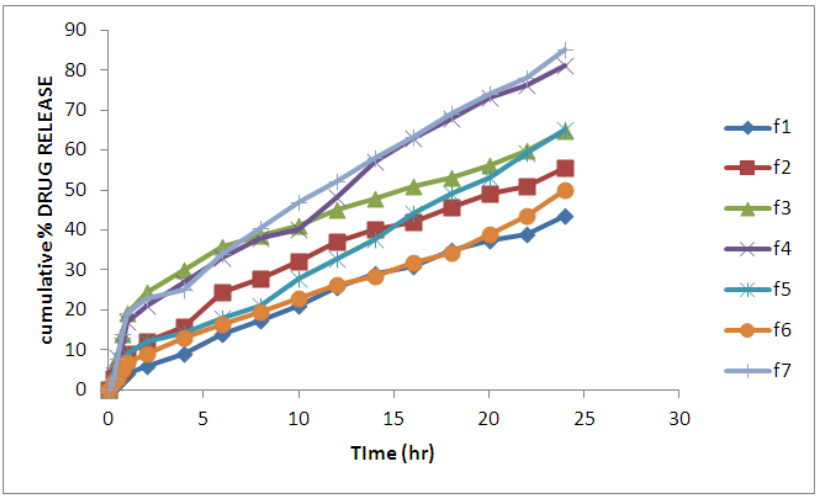


Figure 10: First order graph for membranes F1 to F7

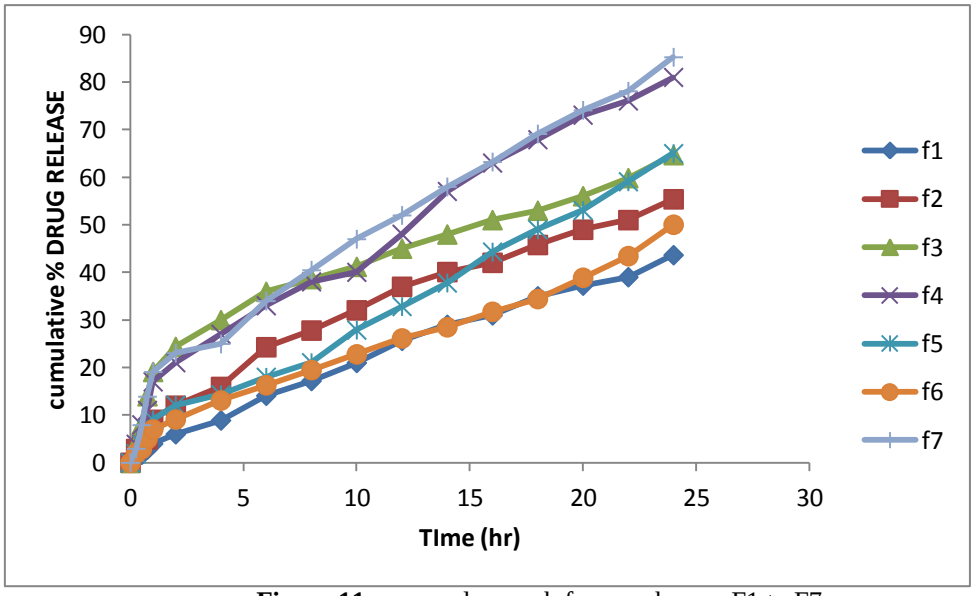


Figure 11: zero order graph for membranes F1 to F7

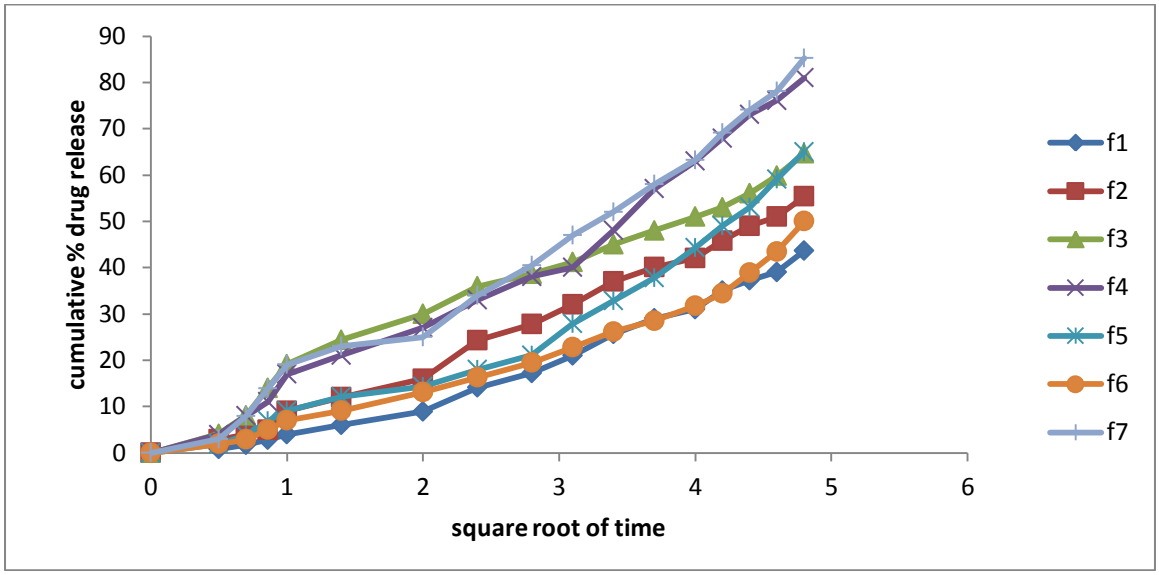


Figure 12: Higuchi's plot for membranes F1 to F7

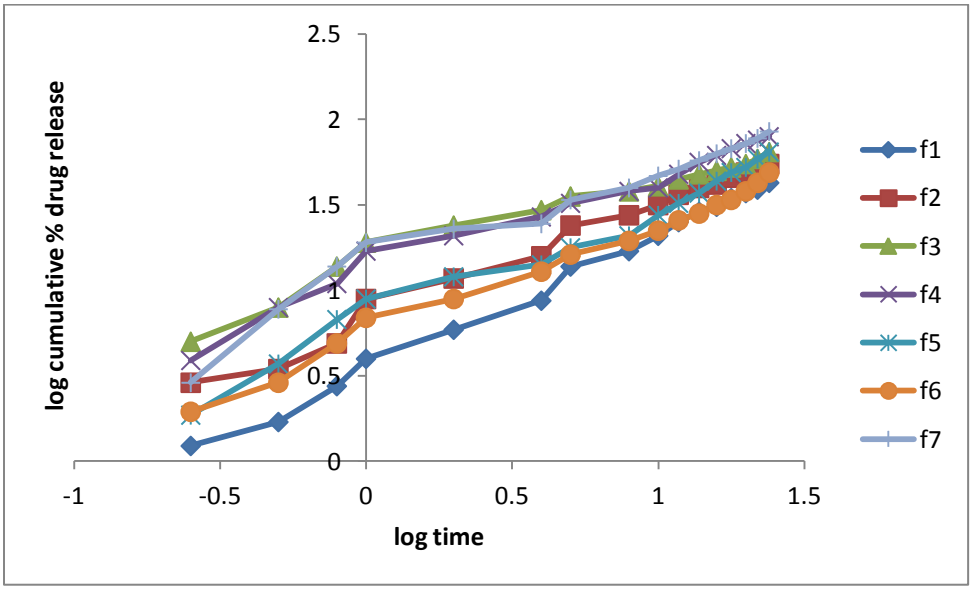


Figure 13: Korsmeyer's peppas plot for membrane F1 to F7

Table 14: Drug permeation kinetics parameters of permeation studies through dialysis membrane.

Formulation code	Zero order plot * (R2)	First order plot * (R2)	Higuchi's plot * (R2)	Korsmeyer's peppas plot *	
				(R2)	n
F1	0.992	0.993	0.979	0.9959	0.796
F2	0.9674	0.9675	0.9919	0.986	0.6657
F3	0.9021	0.9025	0.9837	0.9549	0.4916
F4	0.9747	0.9748	0.9821	0.9765	0.5933
F5	0.9925	0.9925	0.9438	0.9749	0.6928
F6	0.9869	0.9869	0.9824	0.9894	0.6592
F7	0.9712	0.9710	0.9837	0.9456	0.6133

Stability studies

Accelerated stability study: The optimized patches were subjected to stability studies to evaluate any change in the performance when exposed to accelerated conditions of environment during storage, handling transport and use. The patches were packed in the aluminum foil and kept at 40± 2oc and 75 ±5% RH as per ICH guidelines. (ICH Q1A [R2] Stability testing new drugs substances and products)

Table 15: Physicochemical evaluation of best formulation using stability studies

Parameters	0 days*	30 days*		60 days*	
		A	B	C	D
Weight uniformity	37	36.05	36.04	36.02	36.01
Folding endurance	99	99.08	99.05	99.04	99.02
Patch thickness (mm)	0.460	0.458	0.457	0.456	0.455
% Drug content	98.06	98.05	98.04	98.03	98.02
%Moisture Content	2.30	2.97	2.96	2.95	2.94
%Moisture uptake	1.38	1.37	1.36	1.35	1.34
WVTR (gm/cm2/hr)	0.4005	0.4004	0.4003	0.4001	0.4002
Tensile strength(Kg)	0.3240	0.3239	0.3237	0.3238	0.3236
Bursting strength(Kg)	3.025	3.024	3.023	0.322	3.021

Mean (n=3)

*** All values are the mean of three readings ± SD A, C: 30 ± 2°C/ 65 ± 5% RH B, D: 40 ± 2°C/ 75 ± 5% RH.**

IV. Discussion

Development of Calibration Curve

Calibration curve of the pure drug losartan potassium was prepared in the concentration range of 2µg/ml to 10µg/ml at the wavelength of 205.5 nm. The calibration curve showed good linearity and regression coefficient was 0.9975 (r2 value).

Compatibility Study by Differential Scanning calorimetry Analysis

The DSC analysis of losartan potassium alone showed a sharp endothermic peak at273.44 °C corresponding to its melting point (275.85˚C), it indicate that the drug sample was pure. The DSC analysis of losartan potassium with PVA and PVP K30 negligible change in the melting point of Losartan potassium (263.67°C), which indicated that the polymer do not interact with the drug

Infra-Red Spectrophotometry

IR spectrum of pure Losartan potassium physical mixture of Losartan potassium with polymer are shown in Fig 5.2 to 5.6 it indicate that the pure drug Losartan potassium functional group peaks were present in all the formulations with small change in peak position, after incorporated with polymer PVA, PVP K30 and urea as shown in table 5.2 so the result clearly indicates that there is no interaction between the pure Losartan potassium and other excipients.

Evaluation of Transdermal Systems

Thickness And Folding Endurance

Results indicated that the membrane would not break and would maintain their integrity with general skin folding when applied.

Swelling Index

It is found that the swelling index of F1 (45.02) is lowest when compared with F2(57.08), F3 (65.04), F4 (70.1), F5 (82.18), F6(90.12) and swelling index of F7(98.10) was found to be highest when compared to others. Hence the swelling index of membranes was found to be increasedwith increase in concentration PVA.

Moisture Content & Moisture Uptake

The moisture uptake of membranes F3 (1.06), F2 (1.11) F1 (1.21), F6 (1.29) was decreased when compared to F7 (1.38) F4 (1.50) and F5 (1.51) respectively. Moisture content of membranes F1 (2.89), F4 (2.79), F2 (2.38) was increased when compared to F3 (1.94). Moisture content and moisture uptake studies indicated that increase in ratio of PVA resulted in increased moisture content and moisture uptake of the membrane.

Water Vapour Transmission Study

Water vapour transmission studies indicated that all the membranes prepared were permeable to water vapour. The value of permeation coefficient was lowest in F1 (0.3148) and highest in F7 (0.4005). This is due to presence of higher concentration of PVA in F7. The rate of water vapour transmission in different membranes was found to be, decreased in following order F7>F6>F5>F4>F3>F2>F1.

Tensile Strength and Extension

The tensile strength (0.9158) film of membraneF1 was found to be highest, whereas tensile strength (0.3240) of membrane F7 was lowest. The results reveal that the membranes have reasonable tensile.

Bursting Strength

The bursting strength (4.466) of film of membrane F1 was found to be highest, whereas bursting strength (3.3025) of membrane F7 was lowest. As a result the bursting strength of the films decreased with increasing concentration PVA. The results reveal that the membranes have reasonable bursting strength.

***In Vitro* Skin Permeation Studies**

The *in- vitro* release profile is an important tool that predicts in advance how a drug will be have *in-vivo*. When the cumulative amount of drug permeated per square centimeter of patches through dialysis membrane was plotted against time, the permeation profiles of the drug followed first order kinetics. Since many release processes can be represented by a coupling of a Fickian and non-Fickian mechanism, Ritger and Peppas introduced the power law equation. $Mt/M\infty = Ktn$ to characterize the controlled-release behavior of a drug from polymer matrices. The value of 'n' can be calculated from the slope of $InMt/M\infty$ vs. in t and can be indicative ofthe operating release mechanism. The results of *in vitro* skin permeation studies of losartan potassium membranes prepared with different ratios of PVP and PVP K30 (F1 to F7) are shown in Table 14 The cumulative amount of drug permeated from membranes decreased with decrease in amount of PVA. Which results in opening of polymer chain and increasing swelling index, moisture content, moisture uptake, permeation coefficient and results in increased drug permeation. When the cumulative amount of drug permeated per square centimeter of membrane through dialysis membrane was plotted against time, the permeation profiles of the drug followed first order kinetics. The 'n' values more than 0.5 and less than obtained by this equation indicated that the amount of drug permeation followed Anomalous (Non Fickian) diffusion in F1, F2, F3,F4, membranes and F5, F6, F7 membrane follows fickian diffusion.

V. Conclusion

The transdermal route of drug delivery is becoming increasingly popular with the demonstrationof the percutaneous absorption of large number of drugs. The transdermal drug delivery system approaches zero order drug input and performs as a constant intravenous infusion. For thispurpose, the fabrication of TDDS requires suitable matrix systems, rate controlling membranes and drug reservoirs.

Losartan potassium a non-peptide angiotensin II receptor type-1(AT1) antagonist used in management of hypertension was chosen as the model candidate for this study since it possesses near ideal characteristics that a drug must have in formulating a transdermal drug delivery system: low molecular mass, high lipid solubility, effective in low plasma concentration as well as a high degree of first-pass metabolism.

In the present study different polymers PVA, and PVP K30 were used to prepare transdermal system of Losartan potassium. Drug and polymers were subjected for compatibility study using differential scanning calorimetry, which suggested that there was no interaction between drugand polymers.

The results of permeation study indicated that the drug permeation was in controlled fashion. To analyze the mechanism of drug release from the membranes, the *invitro* permeation data were fitted to zero order, first order, Higuchi release model and Korsmeyer and Peppas model. It was observed that the drug permeation followed anomalous (Non Fickian) diffusion in F1, F2, F3 and F5, F6, F7 membrane follows Fickian diffusion.

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