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DESIGN AND EVALUATION OF POLYMERIC FILMS (HPMC) OF ENALAPRIL MALEATE FOR TRANSDERMAL USE

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ABSTRACT

Objective: The aim of the present investigation was to develop medicated and non-medicated transdermal films. **Methods:** Non-medicated films were formulated with different ratios of polymers HPMC K4M and K100M glycerol as a plasticizer, whereas the medicated films were formulated of antihypertensive agent Enalapril maleate using same polymers and plasticizer. The possible drug-polymer interactions and compatibility were studied by FTIR and DSC studies. **Results:** Formulated transdermal films were formulated for various physicochemical characterization, in-vitro diffusion study, stability studies and in-vitro diffusion data was analyzed by using various kinetic models. The results of all physicochemical parameters were found to be within limits. The in-vitro diffusion study was performed using Franz diffusion cell and full thickness rat abdominal skin as a barrier. The in-vitro diffusion data revealed that JK4 formulation batch showed good permeation at the end of 10hrs. **Conclusion:** The physicochemical characterization and permeability studies indicate that the drug & polymers is suitable for Transdermal drug delivery.

KEYWORDS: Transdermal films, HPMC K4M, HPMC K100M, glycerol, Enalapril maleate.

INTRODUCTION

Transdermal drug delivery system provides means to sustain drug release as well as reduce the intensity of action and thus reduce the side effects associated with its oral therapy.[1] Polymers are backbone of TDDS. Advances in the field of polymer science have paved the ways of Transdermal drug delivery system (TDDS) designs that have considerable flexibility.

Transdermal patch consist of special membrane to control the rate at which the drug contained in the reservoir within the patch can pass through the skin and then into bloodstream. Transdermal drug delivery increases patient compliance and avoid first pass metabolism over conventional drug delivery. TDDS established itself as an integral part of novel drug delivery system. TDDS is self-contained; discrete dosage forms which, when applied to the intact skin, deliver drug through the skin at controlled rate to the systemic circulation.[2]

Conditions in which transdermal patches are used[6]

A transdermal patch is used when

1. The patient has intolerable side effects and is requesting another method of drug delivery.
2. The pain control might be improved by reliable administration.
3. It can be used with other enhancement strategies to produce synergistic effects.

Conditions in which transdermal patches are not used[6]

A use of transdermal patch is not suitable when

1. Cure for acute pain required.
2. Rapid dose titration is required.
3. Requirement of dose is equal to or less than 30mg/24hrs.

Care taken while applying Transdermal patch[7]

1. The part of the skin where the patch is to be applied should properly clean.
2. Patch should not be cut because cutting the patch destroys the drug delivery system.
3. Before applying a new patch it should be sure that the old patch is removed from the site.
4. Care should be taken while applying or removing the patch because anyone handling the patch can absorb the drug from the patch.
5. The patch should be applied accurate to the site of administration.

MATERIALS AND METHODS

Enalapril Maleate IP was gift from Suvik, Hitek Pvt. Ltd. Gandhinagar. All other chemicals and reagents used in the study were of analytical grade K4M, K100M (HPMC) Colorcon, Glycerol Pure chem. Sodium chloride Sourav Scientific, Calcium chloride Qualigens, Acetone were used.

Animal Skin used in Research Work

The excised rate skin was preserved further used for present study.

Preparation of Rat Skin

Freshly excised rat skin was isolated and used as the barrier. The full-thickness skin was obtained, epidermis was peeled away from the dermis and washed with water for several times and preserved in saline solution, the following day it was washed several times before use.

METHODOLOGY

Preparation of Transdermal Films[7, 8]

Transdermal films medicated and non-medicated were prepared by mercury substrate method using varying ratio of different grades of polymers and plasticizer.

Films composed of different ratios of HPMC K4M and K100M was prepared by mercury substrate method. HPMC K4M and K100M were weighed and dissolved in 50ml of acetone to form 2.5% w/v solution, and 25%w/w of polymer weight glycerol as a plasticizer was added. This polymeric solution was then placed for agitation. The same polymeric ratios were used for formulating medicated films of Enalapril maleate. The resultant solutions were poured in the glass Petri plate containing mercury as a substrate and allowed to dry at room temperature for 24hrs to obtain the dried films. The films were carefully removed from petridish, checked for imperfection and cut according to the size required for testing. The composition of transdermal films non- medicated & medicated were shown in (table 1) & (table 2) respectively.

Table 1: Composition of Formulation of Non-Medicated Films.

Formulation Design					
Batch	**Polymer concentration**	**HPMC K4M (gm.)**	**HPMC K100M (gm.)**	**Casting solvent**	**Plasticizer (%w/w) Glycerol**
SL1	5:0	1.25	0	Acetone	25
SL2	4:1	1	0.25	Acetone	25
SL3	3:2	0.75	0.5	Acetone	25
SL4	2.5:2.5	0.625	0.625	Acetone	25
SL5	2:3	0.5	0.75	Acetone	25
SL6	1:4	0.25	1	Acetone	25
SL7	0:5	0	1.25	Acetone	25

Table 2: Composition of Formulation of Medicated Films.

Formulation Design						
Batch	**Drug: Polymer Ratio**	**Drug (gm.)**	**HPMC K4M (gm.)**	**HPMC K100M (gm.)**	**Casting solvent**	**Plasticizer (%w/w) Glycerol**
JK1	1:5:0	0.125	1.25	0	Acetone	25
JK2	1:4:1	0.125	1	0.25	Acetone	25
JK3	1:3:2	0.125	0.75	0.5	Acetone	25
JK4	1:2.5:2.5	0.125	0.625	0.625	Acetone	25
JK5	1:2:3	0.125	0.5	0.75	Acetone	25
JK6	1:1:4	0.125	0.25	1	Acetone	25
JK7	1:0:5	0.125	0	1.25	Acetone	25

Evaluation of Transdermal System[16,17]

Mechanical Properties[12,14]

Mechanical properties of polymeric films were determined by measuring there tensile strength.

Tensile strength of the films was determined by using the tensile strength instrument. The film of uniform thickness were cut and placed between two load cell grips and force was gradually applied till the film breaks. The stress-strain curves were recorded for each sample and the tensile strength at breaking point and the percent elongation at break were calculated. The following equations were used to calculate the mechanical properties of the films:-

$$\text{Tensile Strength } (N/m^2) = \frac{\text{Force at Break (N)}}{\text{Initial cross section area of the sample } (m^2)}$$

$$\text{Elastic Modulus } (N/m^2) = \frac{\text{Force at Corresponding Strain (N)}}{\text{Cross section area } (m^2)} \times \frac{1}{\text{Corresponding Strain}}$$

$$\text{Elongation at Break (\%)} = \frac{\text{Increase in Length (cm)}}{\text{Original Length (cm)}} \times \frac{100}{\text{Cross Sectional (cm)}}$$

$$\text{Strain} = \frac{\text{Tensile Strength}}{\text{Elastic Modulus}}$$

Physical Evaluation of Transdermal System[1]

Film Thickness

The thickness of film is measured by using micro meter, electronic vernier callipers, with a least count of 0.01mm, dial gauge or screw gauge. Thickness is five different points on the film and average of five reading is taken.

Figure 1: Vernier Callipers.

Tensile Strength

The strength can be determined by using a modified pulley system. Weight is gradually increased so as to increase the pulling force till the patch breaks. The force required to break the film is considered as tensile strength and it is calculated as kg/cm^2.

$$\text{Tensile Strength} = \text{Tensile } \frac{\text{Load}}{\text{Cross}} \text{ section area}$$

Patch Thickness

Patch thickness can be measured by using digital micrometer screw gauge at three different points.

% Elongation Break Test

The elongation break is to be determined by nothing the length just before the break point. The elongation break can be determined by the formula

$$\text{Elongation Break} = \frac{\text{Final length} - \text{Initial length}}{\text{Initial length}}$$

Percentage of Moisture Content

The films are weight individually and left in desiccators containing anhydrous calcium chloride or activated silica at room temperature for 24 hours. Individually films are weighed

repeatedly until they showed a constant weight. Calculation of % of moisture content is done as the difference between initial and final weight with respect to the final weight.

$$\% \text{ Moisture Content} = \frac{\text{Initial weight} - \text{Final weight}}{\text{Final weight}} \text{X } 100$$

Percentage of Moisture Uptake

A weight film kept in desiccators at room temperature for 24 hours is taken out and exposed to 84% relative humidity (a saturated solution of potassium chloride) in a desiccators until a constant weight for film is obtained. The percentage of moisture uptake is calculated as the differences between the final and initial weight with respect to initial weight.

$$\% \text{ Moisture Uptake} = \frac{\text{Final weight} - \text{Initial weight}}{\text{Initial weight}} \text{X } 100$$

Water Vapour Transmission Rate (WVTR)

Glass vials approximate 5 ml capacity of equal diameter was taken for transmission study. All vials washed thoroughly and dried in an oven completely. Weight about 1 gram of anhydrous / fused calcium chloride and kept in respective vials. Fix the films on the brim of vials and weigh individually the kept in closed desiccator containing saturated solution of potassium chloride to maintain humidity approximate 84%. The vials were weight in 6, 12, 24, 36, 48 and 72 hours respectively.

$$\text{Transmission Rate} = \frac{\text{Final weight} - \text{Initial weight}}{\text{Area X Time}} \text{X } 100$$

Drug Content Determination

The films of size $1cm^2$ were cut and placed in a 100ml volumetric flask containing phosphate buffer 7.4 pH. The contents were stirred using a magnetic beads for 24hrs to dissolve the films. The 1ml was withdrawn from that solution and diluted to 10ml; the absorbance was measured at 207nm. From the absorbance and the dilution factor, the drug content in the film was calculated.

In-Vitro Skin Permeation[18]

To study the in-vitro drug release profile from the prepared TDDS films Franz diffusion cell was used. The elution medium was 20ml of phosphate buffer of 7.4 pH and freshly excised rat skin was used as the barrier. The film was placed in between the donor and receptor

compartment in such a way that the drug releasing surface faced towards the receptor compartment. The receptor compartment was filled with the elution medium and allowed to stir with the help of magnetic stirrer. The temperature of elution medium was maintained and controlled at 37±1°C by a thermostatic arrangement. An aliquot of 1ml was withdrawn at predetermined intervals and also replaced by equal volumes of the elution medium. The concentration in the aliquot was determined spectrophotometrically and was calculated with the help of a standard calibration curve.

Figure 2: Franz Diffusion Cell Apparatus.

Accelerated Stability Studies[13]

The optimized patches were subjected to accelerated stability studies to evaluate any change in the performance when exposed to accelerated conditions of environment during storage. The films were packed in the aluminum foil and kept at 40± 0.5°C and 75 ±0.5% RH as per ICH. The physicochemical parameters and percentage drug release was evaluated before and after stability study.

UV Spectroscopy

The UV spectrum of Enalapril maleate was obtained in pH 7.4 as solvent which showed absorbance maxima at wavelength (λ_{max}) 207 nm.

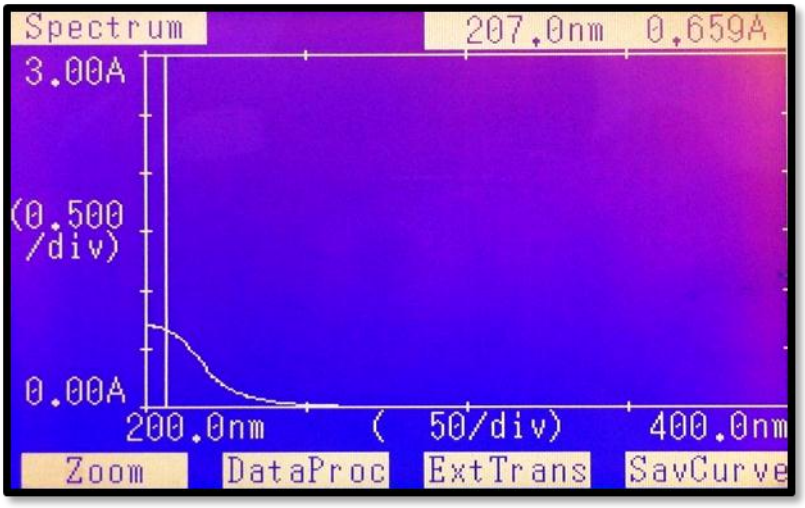

Figure 3: UV Spectra of Enalapril Maleate.

Calibration Curve by UV Spectroscopy

The calibration curve of the Enalapril maleate was prepared in phosphate buffer pH 7.4 the absorbance at λ_{max} 207 nm for different concentration of Enalapril maleate and the calibration curve. The regression coefficient was found to be 0.998 with slope value 0.050 and the y-intercept value 0.009. The results indicated that there is a linear relationship between concentration (1-10mcg/ml) and absorbance.

Table 3: Data of Calibration Curve In Enalapril Maleate.

Sr. No.	Concentration (mcg/ml)	Absorbance at (207 nm)
1	0	0
2	1	0.075
3	2	0.109
4	3	0.159
5	4	0.212
6	5	0.261
7	6	0.311
8	7	0.354
9	8	0.402
10	9	0.46
11	10	0.521

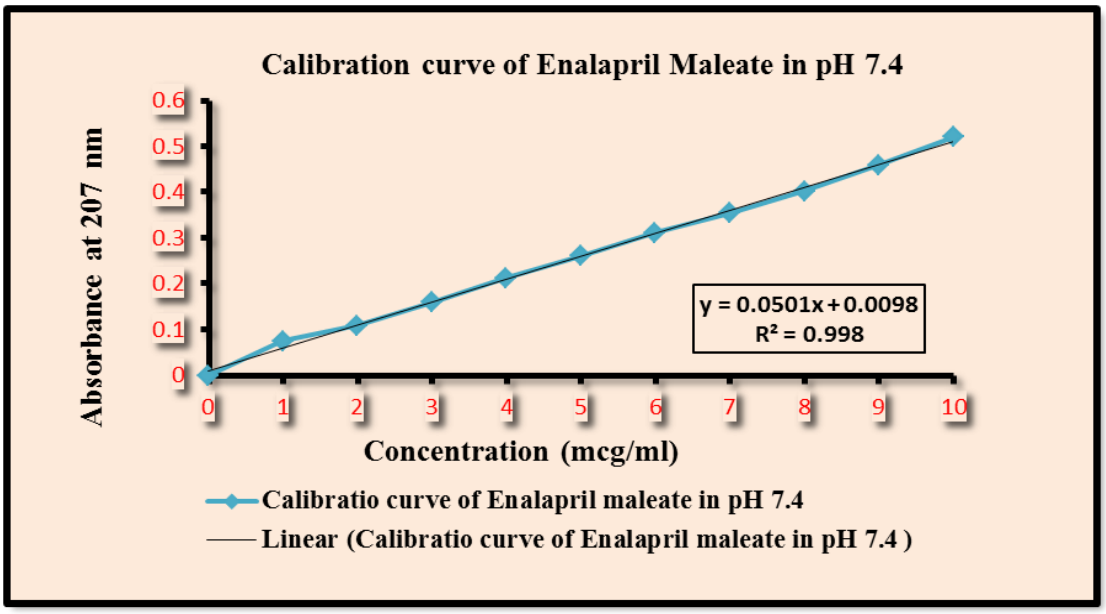

Figure 4: Calibration Curve of Enalapril Maleate.

Drug-Excipients Compatibility Study

FTIR Study

FT-IR spectrum of drug with polymeric films as well as placebo films was recorded as potassium bromide (KBr) pellets at scanning speed 2mm/sec with resolution of 4[1/cm]over the region 4600-350cm^{-1} for its authentication and to study principle peaks using FT-IR spectrophotometer (Shimadzu8400).

DSC Study

The DSC study was carried out for drug with polymeric films as well as placebo films that were expected to be used in the development of formulation. The DSC patterns were recorded on a PerkinElmer 4000 instrument. Each sample (1mg) was heated in crimped aluminium pans at a scanning rate of 10^{0}c/min from 30 to 350^{0}c. Sample analysis was performed under Nitrogen Purging and flow rate was 20ml/min. An empty aluminium pan was used as a reference.

Kinetics of the Drug Release[12]

The results obtained from in-vitro permeation studies were analyzed by various kinetic models to know the mechanism of drug release from the films.

Zero-Order Model

$$\% \text{ Released} = K_o\, t$$

Where, K: the apparent dissolution rate constant or zero order release constant.

Higuchi Model

$$M_t = M_o + K_H \times t^{1/2}$$

Where, M_t: the amount of drug released at time t; K_H: the Higuchi release rate.

Peppas- Korsmeyer Model

$$M_t/M_\alpha = K_{tn}$$

This model is used to describe the drug release mechanism through polymeric system. The 'n' value is used to characterize different release mechanism. The 'n' value is given in the (table 3).

Table 4: Interpretation of Diffusional Release Mechanism for Polymeric Films.

'n' value	Drug Release Mechanism
$0.45 \leq n$	Fickain diffusion
$0.45 < n < 0.89$	Non-fickain diffusion
$n = 0.89$	Case II (relaxation) transport
$n > 0.89$	Super case II transport

RESULTS AND DISCUSSION

Matrix type transdermal films of enalapril maleate were prepared using varying polymer concentrations of HPMC K4M and K100M to get desired drug Release. The transdermal films of enalapril maleate were evaluated for various physicochemical characterization like Thickness, Weight variation ,Tensile Strength, Folding Endurance, Percent moisture content, Percent Moisture Uptake, Water Vapor Transmission Rate (WVTR), Percent Elongation are shown in (Table 5). All the physicochemical characterization results were found to be within the limits. The polymeric films and also the drug loaded films prepared were found to be thin, elastic and transparent.

Table 5: Physicochemical Evaluations for Medicated Films.

Formulation Code	JK1	JK2	JK3	JK4	JK5	JK6	JK7
Thickness	0.10± 0.005	0.11± 0.005	0.11± 0.005	0.12± 0.005	0.11± 0.005	0.12± 0.005	0.11± 0.005
Weight Uniformity	14.67± 1.15	15.78± 0.58	14.33± 0.58	15.22± 0.20	14.4± 0.40	14.2±0.35	15.33± 0.58
Folding Endurance	96.3±6.11	95± 3.00	96± 2.64	83.33± 4.04	100± 5.56	133± 3.51	126± 6.55
Percent Moisture Content	14.43±0.84	09.49± 0.50	7.73± 0.25	25.11± 0.21	11.01± 0.20	12.1± 0.98	9.39± 0.46
Percent Moisture Uptake	22.22±0.87	18.18± 2.45	7.14± 1.68	30± 2.12	9.09± 1.34	16.66± 0.65	12.5±0.46
Water Vapour Transmission Rate (WVTR)	0.0075±0.009	0.0082±0.004	0.0085±0.019	0.0158±0.020	0.0075±0.001	0.095±0.015	0.0081±0.006
Tensile Strength	5.828×10^6	3.311×10^6	0.732×10^6	4.296×10^6	5.566×10^6	4.211×10^6	3.423×10^6
Percent Elongation Break	94±2.36	74± 1.56	185± 0.32	132± 1.12	102±2.41	104± 0.14	166± 0.75

In-vitro Diffusion Study

From the in vitro Diffusion Study data kinetics of drug release was found for zero order (K_0), peppas- Korsmeyer and higuchi(k_h) release kinetics. The in vitro drug release profile

followed peppas- Korsmeyer for better characterization of drug release behavior which predominates over the zero order (K_0) and higuchi (k_h) release kinetics.

The release profile for all formulations was in following order:

JK4>JK5>JK3>JK1>JK2>JK6>JK7>

It seems that EM showed maximum drug release in JK4 film i.e. 47.01%, this could be possible due to the presence of equal proportion of polymer HPMC K4M and K100M (2.5:2.5) . JK5 composed of both polymers in the ratio of (2:3), JK3 (3:2), JK1 (5:0) and JK2 (4:1) showed 45.68%, 43.10%, 33.44%, 30.98% drug release at the end of 8hrs respectively. JK6 composed of both polymers in the ratio of (1:4) and JK7 (0:5) showed 26.15% and 27.94% least drug release at the end of 8hrs respectively among all formulations.

To analyze the release kinetics data various models were used. The regression coefficients calculated for all formulations are tabulated in (table 7).Based on the higher regression value the best fit model was identified.

The formulation JK1, JK2, JK6 and JK7 followed zero order kinetics, whereas JK3, JK4, JK5 followed Peppas korsmeyer model.

The (table 7) shows release kinetics profile of EM films for Zero order, Higuchi model and Peppas korsmeyer model.

Peppas korsmeyer model is used to describe the drug release mechanism through polymeric system. The ‘n’ value is used to characterize different release mechanism.

The results showed that ‘n’ value was found to be more than 0.45 but less than 0.89. So this indicates that the release follows non-fickian diffusion mechanism.

Peppas Korsmeyer Model

Table 6: Peppas Korsmeyer Model Profile for JK1-JK7 Formulation Batches.

Log T	Log % drug release						
	JK1	JK2	JK3	JK4	JK5	JK6	JK7
0.000	0.00	0.00	0.00	0.00	0.00	0.00	0.00
1.778	0.567	0.591	1.097	0.997	1.011	0.601	0.899
2.079	0.889	0.755	1.229	1.182	1.198	0.771	1.045
2.255	1.052	0.971	1.339	1.322	1.350	0.974	1.129
2.380	1.173	1.130	1.390	1.436	1.447	1.087	1.168
2.477	1.297	1.247	1.466	1. 491	1. 506	1.202	1.248
2.556	1.378	1.353	1.516	1.574	1.565	1.279	1.312
2.623	1.451	1.431	1.573	1.623	1.620	1.353	1.372
2.681	1.524	1.491	1.634	1.672	1.660	1.418	1.446
R^2	**0.907**	**0.888**	**0.998**	**0.992**	**0.995**	**0.915**	**0.96**

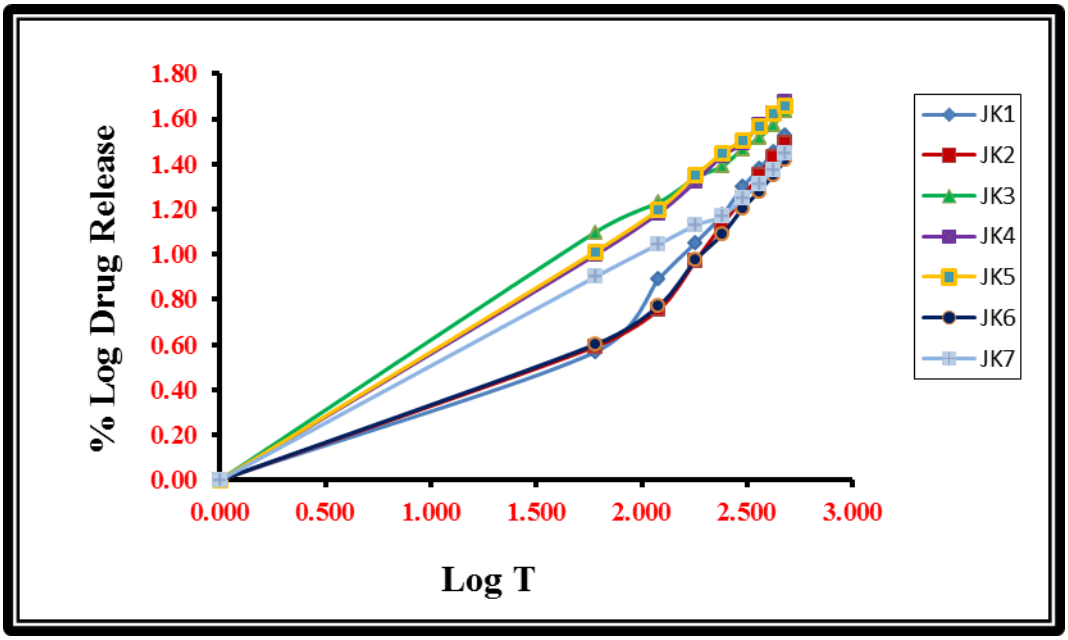

Figure 5: Graph of Log % Drug release Vs Log T for JK1-JK7 Formulation Batches.

Kinetics Data of the Formulation

Table 7: Kinetics data of drug release study.

Formulation Code	Zero Order	Higuchi Model	Peppas Korsmeyer Model	
	R^2	R^2	R^2	n
JK1	0.997	0.891	0.907	0.560
JK2	0.991	0.869	0.888	0.543
JK3	0.967	0.976	0.998	0.595
JK4	0.983	0.970	0.995	0.618
JK5	0.990	0.957	0.992	0.618
JK6	0.997	0.902	0.915	0.516
JK7	0.964	0.960	0.96	0.518

CONCLUSION

Enalapril Maleate, an antihypertensive drug has the average terminal half-life of enalaprilat is 35-38 hours. The effective half-life following multiple doses is 11-14 hours and a bioavailability of 55-75%. It undergoes extensive first pass metabolism. The present study aims to formulate and evaluate Transdermal films Enalapril Maleate. The physicochemical characterization and permeability studies indicate that the drug is suitable for Transdermal drug delivery. The objective of the present study was to develop and evaluate different Transdermal matrix films of HPMC K4M & K100M containing Enalapril Maleate to avoid the hepatic First-pass effect and improve therapeutic efficacy of the drug.

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