Formulation and Development of Eudragit Based Transdermal Matrix Films of Antihypertensive Drug

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ABSTRACT: The aim of the present investigation was to develop medicated and non-medicated transdermal films. Non-medicated films were formulated with different ratios of polymers Eudragit RL100 and Eudragit RS100 and DBP 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. Formulated transdermal films were formulated for various physicochemical characterization, in-vitro diffusion study, stability studies and in-vitro diffusion data was analysed 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 8hrs.

KEYWORDS: Transdermal films, Eudragit RL100, Eudragit RS100, DBP, Enalapril maleate.

I. INTRODUCTION

[1,2]Transdermal patches are innovative drug delivery systems and can be used for achieving efficient systemic effect bypassing hepatic first pass metabolism and increasing the fraction absorbed. Transdermal drug delivery systems (TDDS) allow delivery of contained drug into the systemic circulation via permeation through skin layers at a controlled rate.

[3]These systems are easy to apply and remove as and when desired. The angiotensin converting enzyme inhibitors have become the first line therapy in treating hypertensive patients. It inhibits the conversion of the inactive angiotensin-I to the highly potent vasoconstrictor, angiotensin-II and also reduce the degradation of bradykinin. Most ACE inhibitors are bipeptides that are too hydrophilic to dissolve and penetrate through the lipid layers.

[4]Enalaprilat is poorly absorbed from GIT, thus a prodrug ethyl ester of enalaprilat called enalapril is used. After oral administration, the elimination half-life is <2hrs for unchanged form and average half-life is 35-38 hrs. So an alternative route like transdermal drug delivery system is chosen to deliver the drug to systemic circulation Enalapril was selected among the ACE inhibitors due to molecular size, therapeutic dosage, and the overall lipophilicity of the drug molecules. Prodrug of enalapril is also exhibited a significantly higher transdermal penetration rate. According to BCS classification Enalapril is categorized under class I drug. The objective of the present study was to develop medicated and non-medicated transdermal films in order to improve bioavailability and reduce the dose frequency.

II. MATERIALS AND METHODS

Enalapril maleate was a gift sample obtained from Suvik, Hitek Pvt. Ltd. Gandhinagar, Eudragit RS100 and Eudragit RL100 were obtained from Roehm Pharma Polymers and Dibutyl phthalate (Merck).

III. EXPERIMENTATION
Preparation of Transdermal Films

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 Eudragit RL 100 and Eudragit RS 100 was prepared by mercury substrate method. Eudragit RL100 and Eudragit RS100 were weighed and dissolved in 50ml of alcohol to form 2.5% w/v solution, and 25%w/w of polymer weight DBP 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 were shown in below table.

Formulation Design					
Batch	Polymer concentration	Eudragit RL100 (gm)	Eudragit RS100 (gm)	Casting solvent	Plasticizer (%w/w) DBP
SL1	5:0	1.25	0	Alcohol	25
SL2	4:1	1	0.25	Alcohol	25
SL3	3:2	0.75	0.5	Alcohol	25
SL4	2.5:2.5	0.625	0.625	Alcohol	25
SL5	2:3	0.5	0.75	Alcohol	25
SL6	1:4	0.25	1	Alcohol	25
SL7	0:5	0	1.25	Alcohol	25

Table - Composition of formulation of non-medicated films

Formulation Design					
Batch	Drug: Polymer Ratio	Drug (gm)	Eudragit RL100 (gm)	Eudragit RS100 (gm)	Casting solvent	Plasticizer (%w/w) DBP
JK1	1:5:0	0.125	1.25	0	Alcohol	25
JK2	1:4:1	0.125	1	0.25	Alcohol	25
JK3	1:3:2	0.125	0.75	0.5	Alcohol	25
JK4	1:2.5:2.5	0.125	0.625	0.625	Alcohol	25
JK5	1:2:3	0.125	0.5	0.75	Alcohol	25
JK6	1:1:4	0.125	0.25	1	Alcohol	25
JK7	1:0:5	0.125	0	1.25	Alcohol	25

Table - Composition of formulation of medicated films

IV. CHARACTERIZATION OF TRANSDERMAL PATCHES

[5, 6, 7]Physicochemical characterization

1. Physical appearance

All the transdermal films were visually inspected for clarity, color.

2. Thickness

Thickness of prepared films was measured by Vernier Caliper at three different points and mean values were calculated**.**

3. Weight uniformity

The prepared patches were dried at 60°c for 4hrs before testing. The film of size 1x1cm2 was cut in different parts of the films and weighed in digital balance. The average weight and standard deviation values were calculated from the individual weights.

4. Folding Endurance

Folding endurance was determined manually for the prepared films. A strip of 1x1cm2 was cut and repeatedly folded at the same place till it broke. The number of times the films could be folded at the same place without breaking is folding endurance value.

5. Percentage moisture content

The prepared patches were weighed individually and kept in a desiccator containing fused calcium chloride at room temperature. The film weight was noted when there was no change in the weight of individual patch. The percentage moisture content was determined as

Percentage moisture content
$$= \frac{[\text{Initial weight} - \text{Final weight}]}{\text{Final weight}} \times 100$$

6. Percentage moisture uptake

The prepared patches were weighed individually and kept in a desiccator containing saturated solution of potassium chloride in order to maintain 84% relative humidity. The films were kept until uniform weight was obtained, and then weighed. The percentage moisture uptake determined as

Percentage moisture uptake
$$= \frac{[\text{Final weight} - \text{Initial weight}]}{\text{Initial weight}} \times 100$$

7. Water vapour transmission

For water vapour transmission studies glass vials of equal diameter were used as transmission cells. About 1 g of fused calcium chloride as a desiccant was taken in the vials and the film of 1cm2 were fixed over the brim with the help of an adhesive tape. These preweighed vials were stored in a humidity chamber at an RH of 80 % with the temperature set to 30°C for a period of 24 h. The weight gain was determined every after 24hrs. The amount and rate of WVT was calculated as

Q = WL/S

Where W is gm of water transmitted / 24 h

L is patch thickness in cm

S is surface area in cm2

WVT rate is usually expressed as the number of grams of moisture gained/hr/cm2.

8. [8, 9] Mechanical Properties

Mechanical properties of 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:-

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

$$\text{Elongation at break (\%)}$$
$$= \frac{\text{Increase in length (cm)}}{\text{Original length (cm)}}$$
$$\times \frac{100}{\text{Cross sectional (cm)}}$$

9. Drug-Excipient compatibility 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).

10. 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 100c/min from 30 to 3500c. Sample analysis was performed under Nitrogen Purging and flow rate was 20ml/min. An empty aluminium pan was used as a reference.

11. [10, 11] In vitro permeation Study

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 PH 7.4 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.

[12, 13]Kinetics of the drug release

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

% Released = Ko t

Kis the apparent dissolution rate constant or zero order release constant.

Higuchi Model

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

Where M is the amount of drug released at time t and H K is 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 below table.

'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

[14, 15]Accelerated stability studies

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 aluminium 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.

V. RESULTS AND DISCUSSION

Matrix type transdermal films of enalapril maleate were prepared using varying polymer concentrations of Eudragit RL100 and RS100 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, Watervapor transmission rate, Percent elongation are shown in below table. 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.

Formulation code	JK1	JK2	JK3	JK4	JK5	JK6
Thickness	0.09± 0.005	0.11± 0.005	0.11± 0.005	0.12± 0.005	0.11± 0.005	0.13± 0.005
Weight uniformity	14.67± 1.15	14.78± 0.58	14.33± 0.58	15.22± 0.20	14.4± 0.40	15.2±0.35
Folding Endurance	97.3±6.11	95± 3.00	96± 2.64	83.33± 4.04	106± 5.56	133± 3.51
Percent moisture content	14.43±0.84	10.49± 0.50	7.73± 0.25	25.11± 0.21	11.01± 0.20	15.1± 0.98

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
Water vapour transmission rate	0.0072±0.009	0.0092±0.004	0.0085±0.019	0.0158±0.020	0.0065±0.001	0.0105±0.015
Tensile strength	5.828×10^6	1.311×10^6	0.732×10^6	4.296×10^6	5.566×10^6	5.211×10^6
Percent elongation break	94±2.36	74± 1.56	85± 0.32	132± 1.12	132±2.41	104± 0.14

Table -Physicochemical evaluations for medicated films

In-vitro Diffusion Study

From the in vitro Diffusion Study data kinetics of drug release was found for zero order (K0), peppas-Korsmeyer and higuchi (kh) release kinetics. The in vitro drug release profile followed peppas-Korsmeyer for better characterisation of drug release behaviour which predominates over the zero order (K0) and higuchi (kh) 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 Eudragit RL100 and RS100(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 analyse the release kinetics data various models were used. The regression coefficients calculated for all formulations are tabulated in Table 6. 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 Figure 8.16, 8.17, 8.18 shows release kinetics profile of EM films for Zero order, Higuchi model and Peppas Korsmeyer model respectively.

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

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
R²	**0.907**	**0.888**	**0.998**	**0.992**	**0.995**	**0.915**	**0.96**

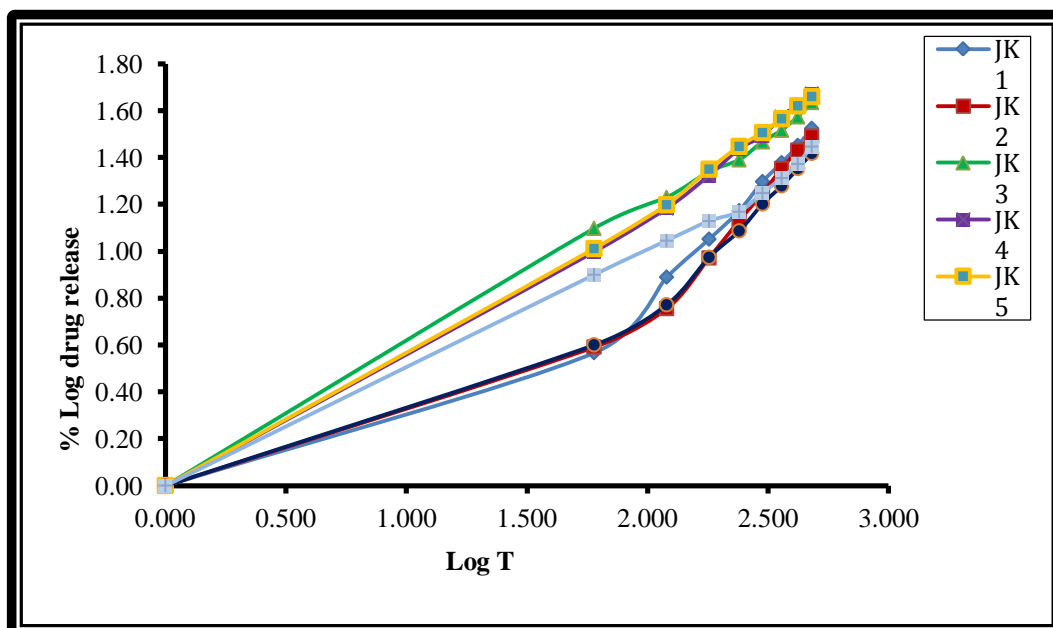**Table - Peppas Korsmeyer Model profile for JK1-JK7 Formulation batches**

Figure - Graph of Log % Drug release Vs Log T for JK1-JK7 formulation batches

Kinetics Data of the formulation

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

Table - Kinetics data of drug release study

[14, 15]Accelerated stability studies
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

VI. CONCLUSION
Enalapril Maleate, an antihypertensive drug has an 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 study indicates 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 Eudragit RS 100 and RL 100 containing Enalapril Maleate to avoid the hepatic First-pass effect and improve therapeutic efficacy of the drug.

films were packed in the aluminium 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.

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