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Research Article

FORMULATION AND EVALUATION OF TRANSDERMAL FILMS OF ENALAPRIL MALEATE

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ABSTRACT
Transdermal drug delivery systems are becoming more popular in the field of modern pharmaceutics. The present study has been carried out to develop matrix type transdermal films containing Enalapril maleate with different ratios of HPMC (hydroxyl propyl methyl cellulose) alone, EC (ethyl cellulose) alone and combination of both HPMC & EC. Propylene glycol 3% is used as plasticizer and span80 is used as permeation enhancer. Formulated transdermal films were evaluated with regard to physicochemical characteristics, in-vitro permeation studies and analysed by using various kinetic models. Kinetic data revealed that the drug release followed first order kinetics and the mechanism of release was found to be non fickian diffusion. The results of the study shows that Enalapril maleate could be administered transdermally through the matrix type TDDS for effective control of hypertension, congestive heart failure and angina pectoris.
KEYWORDS: Enalapril maleate, Transdermal films, HPMC,EC, *In-vitro* drug release study.

INTRODUCTION

Transdermal drug delivery system (TDDS) is a topically administered system in the form of patches or semisolids (gels) that deliver drugs for the systemic effects at a predetermined and controlled rate[1]. Transdermal drug delivery system has many advantages over conventional modes of drug administration, it provides a controlled rate drug release of medicaments, it avoids hepatic metabolism, ease of termination and long duration of action. Study has been carried out to provide an anti-hypertensive drug in transdermal films[2]. The main objective is to evaluate the feasibility of controlled delivery of therapeutically effective amount of drug in matrix type drug delivery. The Transdermal drug delivery system has gained popularity over the fast decades as the major penetration path way of drug molecules through the stratum corneum of human skin by diffusing through lipid envelopes of the skin cells[3].Enalapril is a prodrug that belongs to angiotensin converting enzyme inhibitor class of medicines which has been used for the treatment of hypertension and symptomatic congestive heart failure. After oral administration, the elimination half life is <2 hrs 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 [4].

MATERIALS & METHODS

Enalapril maleate**,** was procured from Yarrow chemicals, HPMC and ethyl cellulose from Lobachemie**,** propylene glycol and Span 80 from Thermo fischer scientific India Pvt.ltd

Preparation of standard graph of enalapril maleate

A spectrophotometric method based on the measurement of absorbance at 206 nm in Phosphate buffer of pH 7.2 was used in the present study for the estimation of Enalapril maleate in the formulations

The standard solution of enalapril maleate was subsequently diluted with phosphate buffer of pH 7.2 to obtain a series of dilutions containing 2, 4, 6, 8 and 10µg of Enalapril maleate in 1 ml solution. The absorbance of these solutions was measured in UV-Vis Spectrophotometer at 206 nm using phosphate buffer of pH 7.2as blank.

Preparation of films

Matrix films are casted on glass mould (petri plate) by solvent casting method. Four types of transdermal films were prepared as per the formula given in the table no:2. All the four formulations contain propylene glycol as the plasticizer and span80 as the penetration enhancer.

Polymers HPMC and EC were dissolved in 20ml of chloroform solvent until it forms a homogenous solution. To this solution required amount of drug was added , and subsequently 0.2% plasticizer (PG) and 3% penetration enhancer (span 80) were added keeping the drug concentration constant in each formulation and stirred continuously to form a homogenous mixture. The entire mixture was poured on to the surface of calibrated petri plate containing mercury as a supporting material

Table:1 List of films prepared.

S.NO	Formulation code	Polymer used
1	EF1	HPMC
2	EF2	EC
3	EF3	HPMC:EC(1:1)
4	EF4	HPMC:EC(3:1)

Table 2: Formulation of transdermal films

Formulation code	Drug(mg)	HPMC(mg)	EC(mg)	PG%w/v	Span 80%w/v
EF1	10	50	-------	0.2%	3%
EF2	10	-------	50	0.2%	3%
EF3	10	25	25	0.2%	3%
EF4	10	75	25	0.2%	3%

EVALUATIONS OF TRANSDERMAL FILMS

PHYSICO-CHEMICAL EVALUATION

Thickness of the film[5-9] :

Thickness of the film was measured by using Screw gauge.

Percentage flatness[5-9]:

Films were cut into the strips, two from either end and one from the centre. The length of these strips was measured to the nearest centimeter without applying any additional pressure. The percentage flatness of the strips were selected as the average percent of length calculated from the strips

Percentage flatness=(Total length of films/average length) X100

Percentage of moisture absorbed[5-9]:

To check the physical stability of the film in high humidity conditions, accurately weighed films were placed in a desiccators containing saturated solution of aluminium chloride (79.5% RH) for three days. The films were re-weighed and the percentage moisture absorption was calculated using the formula.

$$\text{Percentage moisture absorption} = \frac{\text{Final weight - Initial weight}}{\text{Initial weight}} \times 100$$

Weight Uniformity[5-9]:

Ten prepared films are randomly selected and dried at 60°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 .

Folding Endurance[5-9]:

A strip of specific area of film was taken evenly and repeatedly folded at the same place till it broke. The number of times the film could be folded at the same place without breaking gave the value of the folding endurance.

Percentage Moisture lost[10]:

To check the extent of moisture loss from freshly prepared films, accurately weighed films were kept in a desiccator containing fused calcium chloride at room temperature for 72 hrs. After 72 hrs the films were reweighed and determined the percentage moisture loss by the below mentioned formula.

Percentage moisture content = [Initial weight- Final weight/ Intial weight] ×100.

Drug content[11]:

The film of specified area was cut and added to a beaker containing 100 ml of phosphate buffer pH 7.2. The medium was stirred (500 rpm) with teflon coated magnetic bead for 5 hours. The contents were filtered using whatman filter paper and the filtrate was analyzed by U.V. spectrophotometer at 206 nm for the drug content against the blank solution .

In vitro permeation studies[12]:

Carried out by using dialysis set up cellophane membrane was used as semi permeable membrane for diffusion. A weighed amount area (3.14sqcm) of transdermal film was placed on 0one side of membrane. 200ml of phosphate buffer p^H 7.2 was taken as a media in receptor compartment and is maintained at a temperature of 37±0.5ºC. Samples (2ml aliquots) were withdrawn and replaced with same amount of fresh media at appropriate time intervals up to 24 hours and analyzed by UV spectrophotometer. The experiment was performed in triplicate and the mean values were calculated.

Kinetics of the drug release[13]:

To know the mechanism of the drug release from the films, the results obtained from the in-vitro permeation studies were analysed by various kinetic models.

1. Zero order drug release: cumulative % drug release Vs time.
2. First order drug release: log cumulative% drug retained Vs time
3. Higuchi's diffusion equation: cumulative %drug release Vs square root of time
4. Peppaskorsemeyer exponential: log cumulative % drug release Vs log time.

Analysis of release data

The rate and mechanism of release of enalapril maleate from the prepared films were analysed by fitting the release data into zero-order equation, $Q = Q_o - K_o t$ (1), where Q is the amount of drug release at time t and K_o is the release rate; first order equation $\text{Ln } Q = \text{Ln } Q_o - K_1 t$ (2), where K_1 is the release rate constant and Higuchi's equation, $Q = K_2 t^{1/2}$ (3), where Q is the amount of drug released at time t and K_2 is the diffusion rate constant. The release data were also analysed as per Peppa's equation. $M_t/M_\infty = Kt^n$(4), where M_t/M_∞ is the fractional release of the drug, t is the release time, K is a constant incorporating structural and geometric characteristics of the release device, 'n' is the release exponent indicative of mechanism of release. For non-Fickian (anomalous/zero order) release, 'n' value is between 0.5 to 1.0; for Fickian diffusion, $n \leq 0.5$; for zero order release, $n = 1$; for super case transport II, $n > 1$; 'n' is estimated from linear regression of log (M_t/M_∞) Vs log t

RESULTS AND DISCUSSION

The standard curve of enalapril maleate was obtained by taking the absorbance at 206nm, the values are shown in table below and the standard curve of enalapril maleate is plotted by taking concentration on the X- axis and absorbance on the Y-axis and the curve was shown in figure 1.

Table: 3Calibration Curve for the Estimation of Enalapril maleate in phosphate buffer pH 7.2

Concentration(µg/ml)	Absorbance
2	0.15
4	0.30
6	0.44
8	0.60
10	0.75
12	0.89

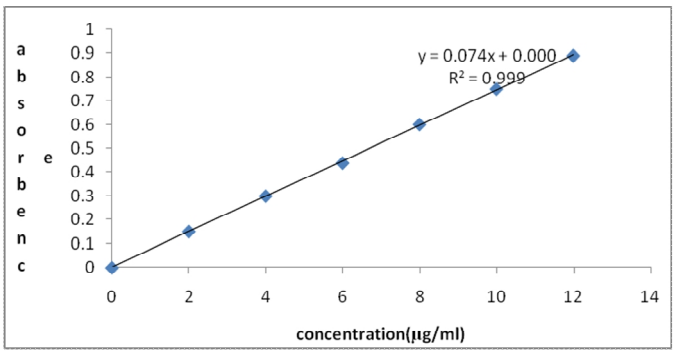

Fig:1 standard calibration curve

Table 4: PHYSICOCHEMICAL EVALUATION

Formulation code	Thickness (mm)	% Flatness	Folding endurance	% Moisture loss	Weight variation	% Drug content
EF1	0.221±0.63	99.9±0.16	146±1.3	1.37±0.62	0..416±0.005	97.3±0.43
EF2	0.241±0.32	100.0±0.43	82±1.7	1.20±0.45	0.156±0.003	97.2±0.56
EF3	0.305±0.11	98.8±0.56	150±1.6	1.16±0.70	0.142±0.003	97.4±0.25
EF4	0.321±0.23	100.1±0.13	162±1.2	1.06±0.46	0.158±0.006	98.8±0.34

Table 5: Correlation coefficient 'r' values in the analysis of release data of transdermal films as per various kinetic models

Formulation code	Zero order	First order	Higuchi	Peppas
EF1	0.9385	0.984	0.961	0.910
EF2	0.9848	0.995	0.995	0.968
EF3	0.928	0.990	0.989	0.946
EF4	0.858	0.947	0.845	0.900

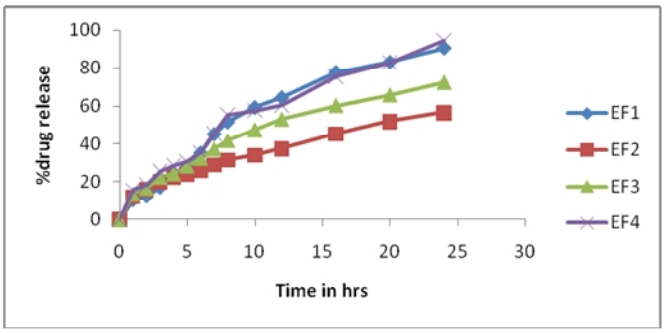

Fig 2: Drug release profile for prepared transdermal films.

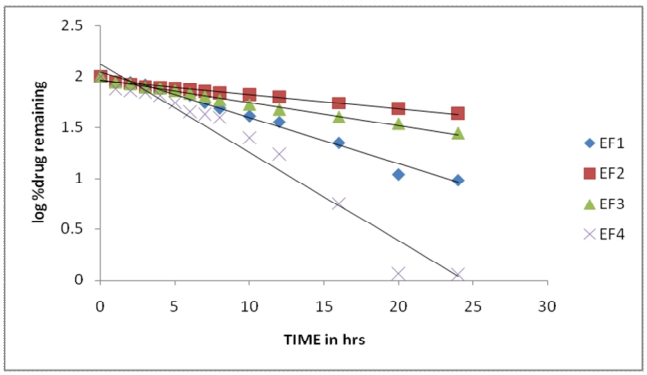

Fig 3: First order plots for transdermal films

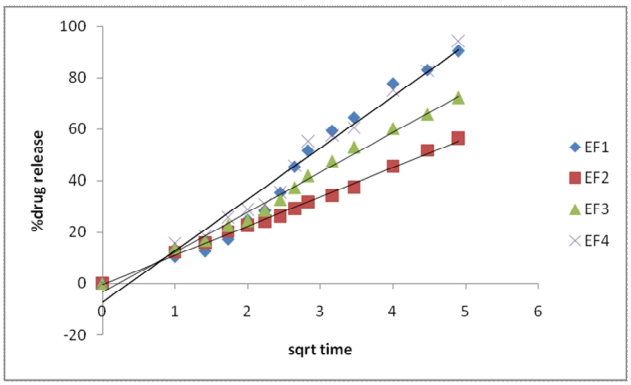

Fig 4: Higuchi plots for transdermal films

DISCUSSION:

Evaluation of transdermal films

The prepared transdermal films were evaluated for their physicochemical characteristics such as weight variation, thickness, folding endurance, % moisture loss, drug content and the results are shown in table 4.

Thickness

The thicknesses of the transdermal films were uniform in all formulations and they were found to be flexible and smooth. The thickness of all the films value ranged from 0.221±0.63to 0.315±0.23as shown in table 4. The results were found to be uniform with low standard deviation value.

Flatness Study

An ideal film should be formulated in such a way that it possesses a smooth surface and it should not constrict with time. Flatness studies were performed to judge the same.

The result of flatness and thickness shown in Table 4 and low value of standard deviation indicates good uniformity. The results of the flatness study showed that none of the formulations had many differences in the strip lengths before and after their cuts indicating good uniformity of the polymers throughout the transdermal films. It indicates much closed to 100% flatness observed in the formulated films. Thus, very minute amount of constriction was observed in the film of any formulation and it indicates smooth flat surface of the films and these formulations can maintain uniform surface when they are applied onto skin.

Folding endurance

The folding endurance measures the ability of film to withstand rupture. The folding endurance was measured manually and results indicated that the films would not break and would maintain their integrity with general skin folding when used. The results of folding endurance are shown in table 4. It was found to be high in patches containing higher amount of the HPMC.

Weight variation

The weight variation of prepared films value ranged from 0.146±0.005 to 0.158 ±0.006. The results were found to be within the limits.

% Moisture loss

The physicochemical study like moisture loss provides the information regarding the stability of the formulation. The results of the moisture content studies for different formulations are shown in table 4. The moisture content varied to a small extent in all prepared films. However, there was an increase in the moisture content with an increase in the hydrophilic polymer, HPMC in matrix transdermal films. The moisture loss of the prepared transdermal films was low, which could help the formulations remain stable and from being a completely dried and reduce brittleness during application.

The percentage moisture loss of the all film value ranged from 1.06±0.46to 1.37±0.62. The results were showed that there was less moisture loss. In all the films, the results revealed that the moisture absorption and loss was found to increase with increasing concentration of hydrophilic polymers. The small moisture loss in the formulations helps the film to remain stable, flexible and free from complete drying. Again low moisture absorption protects the material from microbial contamination and bulkiness of the films.

% Drug content

Drug content was found to be uniform among the all formulations and ranged from 94.3±0.43 to98.8±0.36. The drug content values are found to be within the specified limits.

Drug release studies

Drug release from different films was studied in phosphate buffer of pH7.2.The release profiles are shown in figure 2. Drug release from all the films was slow and spread over a period of 24hrs and depends upon the nature of polymers used in the films.

Analysis of data as per zero order, first order, Higuchi order and peppas equation models to assess the drug release kinetics and mechanism of release from the films. The correlation coefficient r values in the analysis of release data as per different kinetic models are given in table 5.

Analysis of release data as per zero order and first order kinetic models indicated that drug release from the transdermal films followed first order kinetics; correlation coefficient (r) values in the first order model were higher than those in zero order model. When release data were analysed as per peppas equation the release exponent "n" was greater than 0.5 with all the films indicating non fickian diffusion as the release mechanism. Among all the formulations films made of HPMC(EF1) and combination of HPMC and EC (EF4) showed desired release compared to EF2 and EF3.The first order release rate from the films as shown in the table 5 was in the order of EF4>EF1>EF3>EF2.

CONCLUSION

The results of the present study demonstrated that enalapril maleate can be considered for transdermal film containing HPMC and EC polymers combination and span80 as penetration enhancer for sustained release of the drug over a period of 24 hrs for the management of hypertension. It was found that there was an increase in the drug release by increasing the concentration of hydrophilic polymer HPMC. The films prepared by using only HPMC and combination of both EC and HPMC in the ratio of 3:1 has good folding endurance and also it shows desirable drug release and films prepared with only EC has low folding endurance value and also it shows low drug release.

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