FORMULATION AND EVALUATION OF MATRIX TYPE TRANSDERMAL SYSTEM OF LISINOPRIL DIHYDRATE

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INTRODUCTION

Lisinopril is a drug of class angiotensin converting enzyme (ACE) inhibitor that is primarily used in treatment of hypertension, congestive heart failure, heart attacks and also in preventing renal and retinal complications of diabetes. If it is given orally, there may be severe hepatic first pass metabolism as a result there is reduction in the bioavailability (6-60%). In order to increase the bioavailability of the lisinopril, transdermal films were formulated using different polymer combinations such as hydrophilic (hydroxy propyl methyl cellulose: poly vinyl pyrrolidone) and combination of lipophilic- hydrophilic polymers (ethyl cellulose: poly vinyl pyrrolidone) in different ratios. The prepared films were evaluated for thickness, folding endurance, drug content uniformity, tensile strength, percent moisture uptake, percent moisture loss, in-vitro skin permeation study. In-vitro drug release study through sigma membrane indicated that hydrophilic polymer combinations have shown greater drug release than the hydrophilic-lipophilic polymer combinations. By fitting the data into zero order, first order and Higuchi model, it was concluded that drug release from matrix films followed Higuchi model and the mechanism of release was diffusion mediated.

ABSTRACT

Lisinopril is a drug of class angiotensin converting enzyme (ACE) inhibitor that is primarily used in treatment of hypertension, congestive heart failure, heart attacks and also in preventing renal and retinal complications of diabetes. If it is given orally, there may be severe hepatic first pass metabolism as a result there is reduction in the bioavailability (6-60%). In order to increase the bioavailability of the lisinopril, transdermal films were formulated using different polymer combinations such as hydrophilic (hydroxy propyl methyl cellulose: poly vinyl pyrrolidone) and combination of lipophilic- hydrophilic polymers (ethyl cellulose: poly vinyl pyrrolidone) in different ratios. The prepared films were evaluated for thickness, folding endurance, drug content uniformity, tensile strength, percent moisture uptake, percent moisture loss, in-vitro skin permeation study. In-vitro drug release study through sigma membrane indicated that hydrophilic polymer combinations have shown greater drug release than the hydrophilic-lipophilic polymer combinations. By fitting the data into zero order, first order and Higuchi model, it was concluded that drug release from matrix films followed Higuchi model and the mechanism of release was diffusion mediated.

Key words- Transdermal films, Lisinopril dihydrate, hydrophilic, lipophilic polymer, in-vitro drug release.

INTRODUCTION

Currently, transdermal drug delivery is one of the most promising methods for drug application. Increasing number of drugs is being added to the list of therapeutic agents that can be delivered to the systemic circulation via skin. For transdermal products the goal of dosage design is to maximize the flux through the skin into the systemic circulation and simultaneously minimize the retention and metabolism of the drug in the skin. Transdermal drug delivery has many advantages over the oral route of administration such as improving patient compliance in long term therapy, by-passing first-pass metabolism, sustaining drug delivery, maintaining a constant and prolonged drug level in plasma, minimizing inter- and intra patient variability, and making it possible to interrupt or terminate treatment when necessary. Lisinopril dihydrate is a drug of the angiotensin converting enzyme (ACE) inhibitor class that is primarily used for treatment of hypertension, congestive heart failure, heart attack and also in preventing renal and retinal complications of diabetes. If it is given orally, it undergoes severely hepatic first pass metabolism as a result there is a variation in the bioavailability. Hence to increase the bioavailability of the lisinopril dihydrate, transdermal films were formulated by using different polymer combinations such as hydrophilic (Hydroxy propyl methyl cellulose: Poly vinyl pyrrolidone) and combination of lipophilic-hydrophilic polymers (Ethyl cellulose: Poly vinyl pyrrolidone) in different ratios. There are reports describing the use of hydroxy propyl methyl cellulose (HPMC) and ethyl cellulose (EC) in transdermal drug delivery systems as well as other dosage forms for sustaining the release of drugs and HPMC is freely water soluble, whereas EC is hydrophobic. So the transdermal delivery systems were prepared using HPMC and EC to study the effect of hydrophilic and hydrophobic nature of polymer on release of lisinopril dihydrate.

The aims of the present study was to

1) Prepare transdermal patches of lisinopril dihydrate using hydrophilic and hydrophobic polymer
2) Study in-vitro diffusion behavior of prepared transdermal patch formulations by using the combinations of hydrophilic and hydrophobic polymers.

The purpose was to provide the delivery of the drug at a sustained rate across intact skin.
MATERIALS AND METHODS
Lisinopril dihydrate was obtained from Alkem labs, Mumbai and Hydroxy propyl methyl cellulose (HPMC), Poly vinyl pyrrolidone K30 (PVP), Ethyl cellulose, Propylene glycol (PG), Dibutyl phthalate (DBP), methanol, dichloromethane of analytical grade was obtained from S.D. Fine chemicals Pvt. Ltd, Mumbai, India.

Preparation of transdermal patches
Transdermal patches were prepared by the film casting method or the solvent evaporation method of specially designed glass molds. Different combination of polymers like HPMC: PVP and EC: PVP were used for preparation of transdermal patches. Varying proportion of polymers in each pair was dissolved in solvents such as methanol and dichloromethane (DCM) respectively (Table-1). The final concentration of mixture of polymers in each solution was 10%w/v. Solutions were prepared at room temperature using plasticizers as 30% DBP for EC: PVP combination and 30% PG for HPMC: PVP combinations. Drug was incorporated in the polymer solution by continuous stirring on magnetic stirrer. Polymeric solution was poured within a glass mould. The rate of evaporation of solvent was controlled by inverted cup funnel. After 24 hours the dried films were taken out and stored in dessicator until use.

Evaluation of lisinopril patches

Drug content uniformity
Transdermal patches with an area of 1cm² was cut into small pieces and transferred into 100 ml phosphate buffer (pH 7.4) and shaken for 6h to extract the drug. A blank was prepared using a drug-free patch treated similarly. The solutions were filtered through a 0.45μm membrane, diluted suitably and absorbance was measured at 253nm in an UV-Vis spectrophotometer (Shimadzu, Japan)¹⁴.

Thickness and weight variation
The thickness was assessed at six different points of the membranes using digital screw gauge (Mitutoyo Products) and average thickness was calculated. For each formulation, three randomly selected membranes were used. For weight variation test, three membranes from each batch were weighed individually and the average weight was calculated¹⁵.

Determination of tensile strength and percentage elongation
Membrane strip measuring (10 mm x 50 mm) in dimension and free from air bubbles or any other physical imperfections was held in between two clamps positioned at a distance of 3 cm. During measurement, the membrane was pulled by top clamp at a rate of 0.5 mm/sec, to a distance of 5 cm before returning to the starting point. The force and elongation were measured when the membranes broke. The tensile strength and elongation at break were calculated¹⁶.

\[
\text{Breaking force (N)} = \frac{\text{Tensile strength}}{\text{Cross-sectional area of sample (mm}²)}
\]

\[
\text{Elongation (\%)} = \frac{\text{Increase in length at breaking point (mm)}}{\text{Original length (mm)}} \times 100
\]

Folding endurance
The folding endurance was measured manually for the prepared films. A strip of film was cut evenly and repeatedly folded at the same place till it broken. The number of times the film could be folded at the place without breaking indicated the exact value of folding endurance¹⁷.

In - vitro skin permeation study
In the present study, in-vitro release of lisinopril dihydrate from various matrix systems was studied using Keshery-Chien type diffusion cell using sigma membrane. The cell consists of two chambers, the donor and the receptor compartment. The donor compartment was open at the top and was exposed to atmosphere. The receptor compartment was surrounded by a water jacket for maintaining the temperature at 37 ±1°C and it was provided with sampling port. Diffusion media in the receptor compartment was stirred with magnetic needle. The diffusion medium used was phosphate buffer solution. The drug containing film with a support of a backing membrane was kept in the donor compartment and it was separated from the receptor compartment by standard membrane. The donor and receptor compartment hold together using clips of strong grip.
The receptor compartment containing dissolution medium was maintained at 37 ±1°C by circulating the water in outer jacket from organ bath. The diffusion medium was stirred with magnetic needle 2 mm in diameter and 6 mm in length operated by magnetic stirrer, to prevent the formation of concentrated drug solution layer below the standard membrane. At each sampling time the solution in the receptor compartment was completely withdrawn and replaced with fresh phosphate buffer solution. The concentration of the drug was determined by UV- spectrophotometrically at 253nm for the drug content. In-vitro cumulative drug release data for various polymeric films are given in Table-3 and graphically shown in Fig 1-2.

Percentage moisture uptake
The films were weighed accurately and placed in the desiccator containing 100ml of the saturated solution of aluminum chloride, which maintains 79.50% RH. After three days the films were taken out and weighed.

Percentage moisture loss
The films were weighed and kept in the desiccator containing anhydrous calcium chloride, after 3 days, the films were weighed and taken out.

RESULTS AND DISCUSSION

In the present investigation various polymeric transdermal patches of lisinopril dihydrate were prepared by solvent casting technique. The effect of permeability enhancer (PVP K30) on the permeation of drug from HPMC and ethyl cellulose patches was studied. The physicochemical characteristics of the patches of lisinopril dihydrate in the polymeric matrix were satisfactory with respect to weight variation, thickness, folding endurance and tensile strength, percentage moisture uptake and percentage moisture loss. The polymeric combinations showed good film forming properties. Low standard deviation values were found in the patches, which ensured uniformity of thickness of each film. The drug content uniformity was found maximum in A1 (80.27%) when compared to other polymeric combinations (Table-3). The diffusion studies revealed that, as the concentration of the PVP increases the rate of drug diffusion from the patch through the skin decreases. According to the in-vitro diffusion profile, it was found to be that the hydrophilic polymer in combination with the PVP (A1) was found to give good diffusion through the membrane compared to that of hydrophobic polymer (table-3). Hence the patches A1 and S1 were considered for further in-vitro permeation studies. (Table- 3)

CONCLUSION

Matrix type transdermal patches of lisinopril dihydrate were prepared and evaluated. All formulations have shown good physicochemical properties like thickness, weight variation, drug content, folding endurance, moisture loss and moisture uptake. The in-vitro skin permeation studies data have shown that drug release from the patch formulation have been affected by types of polymer and concentration of polymer. Thus, the molecular diffusion through polymer matrix is an effective, simple and reliable means to achieve sustained/controlled release of variety of active agents from the transdermal therapeutic system. The results have given a rational guideline for formulating a sustained release transdermal therapeutic system of lisinopril dihydrate for the effective treatment in hypertension.

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REFERENCES

5. Lisinopril info - rx-list.com


Table-1: Formulation of the Transdermal patches

<table>
<thead>
<tr>
<th>Ingredients</th>
<th>A1</th>
<th>A2</th>
<th>A3</th>
<th>S1</th>
<th>S2</th>
<th>S3</th>
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<tbody>
<tr>
<td>HPMC:PVP</td>
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<td>1:2</td>
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<tr>
<td>EC:PVP</td>
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<td></td>
<td></td>
<td>1:1</td>
<td>1:2</td>
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<td>PG</td>
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<tr>
<td>DBP</td>
<td></td>
<td></td>
<td></td>
<td>30</td>
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<tr>
<td>Methanol:DCM</td>
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<td>1:1</td>
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Table-2: Physical evaluation of transdermal patches

<table>
<thead>
<tr>
<th>Formulation code</th>
<th>Thickness (mm)</th>
<th>% Weight Variation</th>
<th>% Folding Endurance</th>
<th>% percentage moisture uptake</th>
<th>% percentage moisture loss</th>
<th>Tensile strength (kg/mm2)</th>
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<tbody>
<tr>
<td>A1</td>
<td>0.406</td>
<td>14.3</td>
<td>172</td>
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<td>0.724</td>
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<td>A3</td>
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<td>158</td>
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<td>S1</td>
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<tr>
<td>S2</td>
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Table-3: drug release profile of lisinopril transdermal patch

<table>
<thead>
<tr>
<th>Formulation code</th>
<th>% Drug content</th>
<th>% cumulative drug release</th>
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<tbody>
<tr>
<td>A1</td>
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<td>S3</td>
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Table 4: Correlation coefficient of kinetic modeling

<table>
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<th>FORMULATION CODE</th>
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<td>A₂</td>
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<tr>
<td>A₃</td>
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<td>0.993</td>
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<td>0.963</td>
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<tr>
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<td>0.935</td>
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<tr>
<td>S₃</td>
<td>0.946</td>
<td>0.959</td>
<td>0.963</td>
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</table>

Fig 1: *In-vitro* diffusion studies of A₁, A₂ and A₃

Fig 2: *In-vitro* diffusion studies of S₁, S₂ and S₃

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