INTRODUCTION

Transdermal drug delivery system has seen a veritable explosion in the past decades. In the present scenario, very few transdermal patches are commercially available. The lisinopril being an anti-hypertensive drug requires chronic administration. Since the drug has an extensive first pass metabolism. An attempt was made to develop transdermal drug delivery system for patient compliance. Simple drug-matrix dispersion type of transdermal drug delivery system (TDDS) of Lisinopril was designed for prolonged period of maintenance therapy instead of conventional oral dosage forms. Moreover the physicochemical characteristics of Lisinopril also comply with the general requirement for designing a TDDS to a good extent.

Lisinopril is classified as an antihypertensive. It has mean plasma half-life of 2-3 h and only 40% of the orally administered drug reaches the circulation due to hepatic metabolism. The present research was directed to examine the release rate of lisinopril and see the enhancer effect on the flux and enhancement ratio. This study was aimed at developing a suitable film formulation containing lisinopril for transdermal use; the embedded drug should be released without any preferential binding to the polymer.

There has been a giant leap by the pharmaceutical industry with respect to innovations in the new drug delivery arena in the past two decades. These innovations and changes in strategy present newer challenges and brighter opportunities for the application of new methodologies in the drug delivery process. Drug delivery through intact skin is of utmost importance for controlled release of drug for their extended and safe use, which is yet to be successfully used for a large number of drugs. Formulations on skin can be classified into two...
categories according to the target site of action of the containing drugs. One has systemic action after drug uptake from the cutaneous microvascular network and the other exhibits local effects in the skin. The current study focuses on the drug release kinetics from the rate limiting membrane by varying the type of solvent used, polymeric films and drug loading in transdermal delivery systems.

This search and investigation is expected to add extensively to the existing knowledge and information in the field of proper drug regimen and maintenance therapy of schizophrenia with controlled release TDDS of lisinopril.

MATERIAL AND METHODS

The Hydroxy propyl methylcellulose was supplied by S.P. Pharmaceuticals USA. Polyvinylpyrrolidone (PVP K-30) was obtained from S.d.fine chemicals, Bombay. Dibutyl Phthalate was procured from Central drug house ltd, New Delhi. Chloroform was obtained commercially from Ranbaxy fine chemicals, New Delhi. Hyaluronidase was obtained from Charles pharma ltd. Polyethylene glycol 400 and sodium chloride was purchased from S.d. fine chemicals, Bombay, India. Lisinopril was received as a gift sample from Torrent pharmaceuticals, Ahmedabad.

Preparation of transdermal patches

The TDDS composed of different ratios of HPMC and PVP containing Lisinopril (6mg/cm²) were prepared using anumbra petridish by solvent evaporation technique. The Dibuthyl phthalate was incorporated as a plasticizer at concentration of 30% w/w of dry weight of polymer and 4% of Hyaluronidase was incorporated as a permeation enhancer. Backing membrane was cast by Pouring and then evaporating 4% aqueous solution of polyvinyl alcohol in petridish covered on one side with aluminum foil, at 60° for 6 h. The matrix was prepared by pouring the homogenous dispersion of drug with different blends of HPMC with PVP in chloroform on the backing membrane in petridish. The above dispersion was evaporated slowly at 40° for 2 h to achieve a drug polymer matrix patch. The dry patches were kept in desiccators until use.

<table>
<thead>
<tr>
<th>Formula</th>
<th>Polymeric blend</th>
<th>Drug mg/cm²</th>
<th>Ratio (W/W)</th>
<th>Plasticizer Dibutyl phthalate (30%)</th>
<th>Permeation enhancer Hyaluronidase</th>
<th>Solvent System</th>
</tr>
</thead>
<tbody>
<tr>
<td>HL1</td>
<td>HPMC: PVP</td>
<td>10</td>
<td>3:2</td>
<td>30%</td>
<td>1%</td>
<td>Water</td>
</tr>
<tr>
<td>HL2</td>
<td>HPMC: PVP</td>
<td>10</td>
<td>2:3</td>
<td>30%</td>
<td>1%</td>
<td>Water</td>
</tr>
<tr>
<td>HL3</td>
<td>HPMC: PVP</td>
<td>10</td>
<td>1:2</td>
<td>30%</td>
<td>1%</td>
<td>Water</td>
</tr>
<tr>
<td>HL4</td>
<td>HPMC: PVP</td>
<td>10</td>
<td>2:1</td>
<td>30%</td>
<td>1%</td>
<td>Water</td>
</tr>
<tr>
<td>HL5</td>
<td>HPMC: PVP</td>
<td>10</td>
<td>1:4</td>
<td>30%</td>
<td>1%</td>
<td>Water</td>
</tr>
<tr>
<td>HL6</td>
<td>HPMC: PVP</td>
<td>10</td>
<td>4:1</td>
<td>30%</td>
<td>1%</td>
<td>Water</td>
</tr>
</tbody>
</table>

Preparation of barriers: Human cadaver skin

The fresh, full thickness (75-80 µm) human cadaver skin (of thigh region) of both sex and age group 20-45 years was obtained from the postmortem department of forensic medicine, Victoria hospital. The skin was immersed in water at 60° for a period of 5 min. The epidermis was peeled from the dermis after the exposure. The isolated epidermis (25 ± 5µm) was rapidly rinsed with hexane to remove surface lipids, rinsed with water and then either used or stored frozen (for not more than 48 h) wrapped in aluminium foil.
Spectrophotometer UV/VIS analysis
Lisinopril was determined using Shimadzu UV spectrophotometer at 258 nm. The standard plot indicates a slope of 0.0351 and $R^2$ of 0.9999.

Drug-Excipient interaction study
FTIR spectra of Lisinopril, Hydroxy propyl methyl cellulose, PVP, transdermal film loaded with drug and adjuvants were taken using Perkin-Elmer FTIR spectrophotometer (model 1600- KBr disk method). 50 mg of sample and 150 mg potassium bromide were taken in a mortar and triturated. The triturated sample was kept in a holder and scanned between 400 to 4000 cm$^{-1}$. Here the patches of specified size were taken directly for the study.

Scanning electron microscopy
The external morphology of the transdermal patch was analyzed using a scanning electron microscope (JMS 6100 JEOL, Tyko, Japan). The samples placed on the stubs were coated finally with gold palladium and examined under the microscope.

Differential scanning calorimetry
Thermogram of Lisinopril and preparation of patches were recorded using a Differential scanning calorimetry and were compared. The samples were hermetically sealed in flat-bottomed aluminum pans and heated over a temperature range of 40-240$^\circ$ at a rate of 10$^\circ$/min using alumina as a reference standard.

Thickness determination
The aim of the present study was to check the uniformity of thickness of the formulated films. The thickness was measured at five different points of the film. Using BAKER Digital caliper the average of five readings were calculated.

Uniformity of weight
Five different patches of the individual batch were weighed and the average weight was calculated. The individual weight should not deviate significantly from the average weight of five. The tests were performed on films, which were dried at 60$^\circ$ for 4 h prior to the testing.

Moisture content
The film was weighed and kept in dessicator containing calcium chloride at 40$^\circ$ and dried for at least 24 h. The film was weighed until it showed a constant weight. The moisture content was the difference between the constant weight taken and the initial weight and was reported in terms of percentage (by weight) moisture content.

Flatness
The Longitudinal strips were cut out from the prepared medicated film. The length of each strip was measured and then variation in lengths due to the non-uniformity in flatness was measured. Flatness was calculated by measuring constriction of strips and a zero percent constriction was considered to be equal to a hundred percent flatness.

$$\text{Constriction} (%) = \frac{L_1 - L_2}{L_2} \times 100 \quad \text{...(5)}$$

where $L_1$ = Final length of each strip and $L_2$ = initial length of each strip.

Table 2: Characterization of lisinopril- hydroxy propyl hydroxy propyl methyl cellulose and pvp polymeric films.

<table>
<thead>
<tr>
<th>S. No.</th>
<th>Formulation code</th>
<th>Thickness (n=5)(mm)</th>
<th>Weight variation (n=5)(mg)</th>
<th>Percentage of elongation (n=5)</th>
<th>Tensile strength (n=5)(gm/cm$^2$)</th>
<th>Drug content 1cm$^2$patch (n=3)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>HL1</td>
<td>0.21</td>
<td>19</td>
<td>100%</td>
<td>14.01</td>
<td>95.66%</td>
</tr>
<tr>
<td>2</td>
<td>HL2</td>
<td>0.20</td>
<td>20</td>
<td>100%</td>
<td>13.86</td>
<td>97.60%</td>
</tr>
<tr>
<td>3</td>
<td>HL3</td>
<td>0.19</td>
<td>19</td>
<td>100%</td>
<td>13.48</td>
<td>98.66%</td>
</tr>
<tr>
<td>4</td>
<td>HL4</td>
<td>0.22</td>
<td>19</td>
<td>100%</td>
<td>13.98</td>
<td>98.00%</td>
</tr>
<tr>
<td>5</td>
<td>HL5</td>
<td>0.21</td>
<td>19</td>
<td>100%</td>
<td>14.08</td>
<td>98.66%</td>
</tr>
<tr>
<td>6</td>
<td>HL6</td>
<td>0.20</td>
<td>20</td>
<td>100%</td>
<td>14.20</td>
<td>96.16%</td>
</tr>
</tbody>
</table>
Moisture uptake

A weighed film kept in a dessicator at 40° for 24 h was taken out and exposed to different relative humidities of 75% (saturated solution of sodium chloride) and 93% (saturated solution of ammonium hydrogen phosphate) respectively, at room temperature. Then the weights were measured periodically to constant weights.

Determination of Tensile strength

The tensile strength was determined by using computerized precisa bottom loading balance with necessary modifications. 1 x 1 cm patch was taken and subjected to studies.

Drug content determination of film

Four pieces of 1 cm² each (1 cm x 1 cm) were cut from different parts of the film. Each was taken in separate stoppered conical flasks containing 100 ml of suitable dissolution medium (0.1 N HCL: methanol mixture) and stirred vigorously for 6 h using magnetic stirrer. The above solutions were filtered and suitable dilutions were made. Absorbance was observed using Shimadzu 160A, UV visible recording spectrophotometer at their respective wavelengths, against a blank solution which was prepared by following the same procedure containing the patch without drug.

In Vitro Diffusion Study:

The Franz diffusion cell was used for the study of in vitro release patterns from the prepared TDDS formulations. The Elution mediums of 20% PEG 400 in normal saline, and epidermis of the fresh human cadaver skin excised from the thigh portion was used as the barrier. The films were 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, a small bar magnet was used to stir the medium at a speed of 60 rpm with the help of a magnetic stirrer. The temperature of the elution medium was maintained and controlled at 37±1° by a thermostatic arrangement. An aliquot of 1 ml withdrawn at predetermined intervals, being replenished by equal volumes of the elution medium was carried out for a period of 24 h. The drug concentration in the aliquot was determined spectrophotometrically and was calculated with the help of a standard calibration curve.

Data analysis

The pharmaceutical dosage forms that do not disaggregate and release the drug slowly (assuming that area does not change and no equilibrium conditions are obtained) could be represented by Zero order kinetic equation. Hixson and Crowell (1931) recognized that the particle regular area is proportional to the cubic root of its volume. Colombo et al suggested that the quantity of drug from the matrix type delivery system is often analyzed as a function of the square root of time, which is typical for system where drug release is governed by pure diffusion. However this relationship in transdermal system is not justified completely as such systems can be erodible. Therefore, analysis of drug release from transdermal system must be performed with a flexible model that can identify the contribution to overall kinetics. An equation proposed by Korsmeyer– Peppas for finding out the mechanism of drug release from patches of the dissolution-diffusion data obtained from the above experiments were treated with the different release kinetic equations.

Table 3: Determination of moisture content of different formulation (n=5)

<table>
<thead>
<tr>
<th>S. No.</th>
<th>Formulation code</th>
<th>Ratio</th>
<th>Average moisture content (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>HL1</td>
<td>3:2</td>
<td>3.1468</td>
</tr>
<tr>
<td>2</td>
<td>HL2</td>
<td>2:3</td>
<td>3.8902</td>
</tr>
<tr>
<td>3</td>
<td>HL3</td>
<td>1:2</td>
<td>4.2168</td>
</tr>
<tr>
<td>4</td>
<td>HL4</td>
<td>2:1</td>
<td>2.8680</td>
</tr>
<tr>
<td>5</td>
<td>HL5</td>
<td>4:1</td>
<td>2.1476</td>
</tr>
<tr>
<td>6</td>
<td>HL6</td>
<td>1:4</td>
<td>4.8862</td>
</tr>
</tbody>
</table>

Zero order release equation:

\[ Q = k_0 t \] \hspace{1cm} \text{...(6)}

Higuchi’s square root of time equation

\[ Q = k_t t^{1/2} \] \hspace{1cm} \text{...(7)}
First order release equation;

\[ \log Q_t = \log Q_0 + \frac{Kt}{2.303} \quad \text{(8)} \]

Korsmeyer–Peppas equation;

\[ F = \left( \frac{M_t}{M} \right) = K_m t^n \quad \text{(9)} \]

Where \( Q \) is amount of drug release at time \( t \), \( M_t \) is drug release at time \( t \); \( M \) is total amount of drug in the dosage form, \( F \) is fraction of drug release at time \( t \). \( K_0 \) is zero order release rate constant, \( K_H \) is Higuchi square root of time release rate constant, \( K_m \) is constant dependent on geometry of dosage form and \( n \) is diffusion exponent indicating the mechanism of drug release. If the cylinder value of \( n \) is 0.5, it indicates fickian diffusion, between 0.5 and 1.0 indicate anomalous transport, 1.0 indicates case-II transport and higher than 1.0 super case-II transport.

**RESULTS AND DISCUSSION**

The matrix type transdermal films of Lisinopril were prepared by solvent evaporation technique using combination of hydrophilic and lipophilic polymer. PVP is added to an insoluble film former, HPMC that tends to increase its release rate. The resultant can be contributed to the leaching of soluble component, which leads to the formation of pores and then decrease in the mean diffusion path length of the drug molecules. PVP acts as a nucleating agent that retards the crystallization of the drug and enhances the solubility of the drug in the matrix by sustaining it in an amorphous form.

The spectra of lisinopril was shown to exhibit the peaks at 3555 cm\(^{-1}\) for N-H stretching, 3289 cm\(^{-1}\) for aromatic olefinic C-H stretching, 1656 cm\(^{-1}\) for C=O stretching vibrations, 1611 cm\(^{-1}\) for N-H bending vibrations, 1455 cm\(^{-1}\) for CH\(_2\) (alkyl).
bending vibrations, 2642 cm$^{-1}$ for OH- stretching of –COOH and 1232 cm$^{-1}$ for C=O stretching of carboxylic acid. The spectra of lisinopril with HPMC & PVP was shown to exhibit the peaks at 3553.2 cm$^{-1}$ for N-H stretching, 3289 cm$^{-1}$ for aromatic olefinic C-H stretching, 1656 cm$^{-1}$ for C=O stretching vibrations, 1611 cm$^{-1}$ for N-H bending vibrations, 1455 cm$^{-1}$ for CH$_2$ (alkyl) bending vibrations, 2642 cm$^{-1}$ for OH- stretching of –COOH and 1232 cm$^{-1}$ for C=O stretching of carboxylic acid.
A good tensile strength was found in all the films ranging from 13.50 to 15.00 gm/cm². Drug distribution was found to be uniform in the polymeric films and its content was found to be 98.66 to 94.16 % per cm² in the transdermal drug delivery system.

**The diffusion data of most formulations fitted well into higuchi’s release kinetics**

The data treatment of the release profile was done in korsmeyer peppa’s model indicating values of diffusion co-efficient obtained ranging from 1.0824 to 2.00, the mechanism of drug release in this cases were found to be anomalous transport mechanism i.e., the drug was released by initial swelling and follows anomalous transport, in this study most of the formulations follows the higuchi’s square root release kinetics (KH-25.168-46.828) and ($r^2$-0.9897-0.9975).

The formulations shows linearity on Q vs square root of time plots confirming square root kinetics. The release rate increased with increase of PVP in HPMC polymer combinations, at high PVP  concentration the initial release rate increased gradually which slow down with time.

Normally the patches follow higuchi’s kinetics where the permeability rate slows down as time proceeds

The drug molecule from the surface of the patch dissolves fast & hence the initial rates are high. In this system, the patches were put into parallel combination with skin, the skin being rate controller. The rate decreases further in the later hours.

The stability studies were performed for optimized formulation and were found that formulation was stable for 6 weeks at 25°/ 60% RH. The formulations were found to be stable in terms of physicochemical properties, drug content and drug release.

**Conclusion**

In this study, different ratio of HPMC and PVP transdermal Lisinopril patches were formulated using 4% Hyaluronidase as a permeation enhancer. It can be reasonably concluded that lisinopril can be formulated into transdermal polymeric patches to prolong its release characteristics. Thus the formulation HL 1 (HPMC: PVP, 1:2) was found to be the best for a sustained release once a day formulation. PVP acts as a nucleating agent that retards the crystallization of drug & thus plays a significant role in improving the solubility of the drug in the matrix by sustaining the drug in amorphous form. It undergoes rapid solubilization by penetrating into the dissolution medium. Thus PVP was incorporated into films using mixture of other polymers & the suitability of the films was studied.

The transdermal drug delivery system of Lisinopril was prepared using solvent casting method. In this we can obtain a film of good quality in both physical & chemical characteristics and method was found to be cost effective. The permeability studies, diffusion studies & physicochemical characteristics of formulated films indicated that hyaluronidase is a good enhancer for transdermal drug delivery systems.

The kinetic release pattern of formulation studied showed that the formulation of HPMC:PVP

**Table 4: Determination of moisture uptake (in wt%) of different formulations**

<table>
<thead>
<tr>
<th>S.No</th>
<th>Formulation code</th>
<th>Ratio</th>
<th>Relative humidity 75%</th>
<th>Relative humidity 93%</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>HL1</td>
<td>3:2</td>
<td>6.293</td>
<td>12.234</td>
</tr>
<tr>
<td>2</td>
<td>HL2</td>
<td>2:3</td>
<td>7.698</td>
<td>13.286</td>
</tr>
<tr>
<td>3</td>
<td>HL3</td>
<td>1:2</td>
<td>8.618</td>
<td>13.918</td>
</tr>
<tr>
<td>4</td>
<td>HL4</td>
<td>2:1</td>
<td>5.848</td>
<td>9.648</td>
</tr>
<tr>
<td>5</td>
<td>HL5</td>
<td>4:1</td>
<td>5.141</td>
<td>9.016</td>
</tr>
<tr>
<td>6</td>
<td>HL6</td>
<td>1:4</td>
<td>9.086</td>
<td>14.247</td>
</tr>
</tbody>
</table>
(1:2) with enhancer (Hyaluronidase) was the best with respect to physicochemical parameters and release patterns.

Thus the formulation of transdermal drug delivery system of Lisinopril with above said polymer with enhancer can be used to get the optimum release kinetics.

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REFERENCES