Development and Evaluation of Matrix Type Transdermal Patch of Pravastatin Sodium

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Abstract

Pravastatin sodium is a drug of choice in treatment of hypercholesterolemia. It shows low oral bioavailability (17%) and its plasma half-life is 1-1.5 hrs. Transdermal drug delivery system was selected for the delivery of drug to avoid first pass metabolism and to enhance bioavailability. Patches were formulated using polymer HPMC K15M, guar gum, HPMC K15M with Eudragit RL100 at different concentrations by solvent casting method. Prepared patches were evaluated for thickness, weight variation, surface pH, folding endurance, swelling index, % moisture loss, % moisture absorption, in-vitro and ex-vivo drug permeation, in-vitro dissolution, drug content and FTIR study. HPMC K15M with Eudragit RL100 patch exhibits less moisture absorption, moisture loss and swelling which contribute to retardation of drug release from the patch. While the patch prepared from hydrophilic polymers (HPMC K15M, guar gum) had shown more moisture absorption and swelling. This leads to increase in the drug release from the patch. Formulation G6 (Guar gum 100mg) was selected as optimized batch as it has shown controlled drug release profile of 89.35±1.67% through cellophane membrane, 91.57±1.98% through egg membrane and 87.01±1.94% in ex-vivo study. Kinetic treatment of drug release data revealed that the patch followed Higuchi matrix model.

Keyword: Patch; HPMC; Pravastatin; Guar gum; Transdermal

1. Introduction

Administration of conventional oral dosage forms like tablet, capsule and liquids oral suffers a setback due to problem of local irritation, first pass metabolism and degradation of drug by gastro intestinal tract enzymes. The bioavailability as well as duration of action is reduced by oral administration and thus needs frequent administration. This in turn is associated with the problem of patient compliance to therapy and economy of the treatment. Controlled drug delivery is an approach to deliver the drug into systemic circulation at a predetermined rate. Our body system
should duplicate continuous intravenous infusion, which not only bypasses hepatic first pass elimination but also maintains a constant, prolonged and therapeutically effective drug level in the body. This is made possible by using intact skin as a port of drug administration to provide continuous delivery of drug into systemic circulation. Following skin permeation, the drug first reaches systemic circulation. The drug molecules are then transported to the target site, which could be relatively remote from the site of administration, to produce therapeutic action (Patel et al., 2012; Saroha et al., 2011; Jain et al., 2010; Keleb et al., 2010; Sowmya et al., 2012; Chandrashekar et al., 2008; Soni et al., 2009).

Today's world is facing obesity as the biggest problem, which occur due to presence of hypercholesterolemia. Progression of this leads to generation of cardiovascular disease (CVD). CVD is the single most common cause of death. Approximately 50% of these deaths caused due to CHD and 25% from stroke. Statin therapy is recommended as part of the management strategy for the primary prevention of CVD for adults who have a 20% or greater risk of developing CVD. Five statins currently have marketing authorization as atorvastatin, fluvastatin, pravastatin, rosuvastatin and simvastatin. All statin act by inhibiting 3-hydroxy-3-methylglutaryl coenzyme A (HMG CoA) reductase, an enzyme involved in cholesterol synthesis. Inhibition of HMG CoA-reductase lowers LDL-C levels by slowing down the production of cholesterol in the liver and increasing the liver’s ability to remove the LDL-C already present in the blood and is not free from biopharmaceutics and pharmacokinetic problems of absorption, hepatic metabolism and poor bioavailability.

Pravastatin sodium is 3,5-dihydroxy-7-[6-hydroxy-2-methyl-8-(2 methyl butanoyloxy)-1,2,6,7,8,8a-hexahydonaphthalen-1-yl]-heptanoic acid. It is administered orally in 10, 20, or 40 mg as a single dose daily. Approximately 34% of the drug is absorbed orally out of which the average systemic bioavailability of pravastatin sodium is only 17%. These figures indicate that approximately half of the absorbed drug is subjected to pre-systemic metabolism in the liver. The plasma half-life of drug is 1.5hr. The presence of food in the gastrointestinal tract reduces the bioavailability by about 35–40%. Also, drug is reported to be unstable in acidic pH. These all needs the drug to formulate in a system which increases its bioavailability and half-life in the body. Design and development of transdermal patches of pravastatin sodium will eliminate problems associated with the drug. (Shidhaye et al., 2010; Pinate et al., 2012; Garg et al., 2011; The Japanese Pharmacopoeia 2012)

2. Material and Methods

2.1 Materials

Pravastatin sodium was gift sample from Mylan Laboratories Ltd Nashik. HPMC K15M was gift from Colorcon Asia Pvt. Ltd.. Eudragit RL 100 was gift from Evonik Ltd. Guar gum was gift from Vapi care Pharma. Ltd. All other chemical and reagent were of analytical grade.

2.2 Characterization of Pravastatin sodium (Balaji et al., 2009)

a) UV spectrophotometer (UB Varian Cary 100) was used for preparation of calibration curve, drug content and % drug release. The method was validated for accuracy (recovery test), precision, linearity, limit of detection (LOD) and limit of quantitation (LOQ).
b) FTIR spectroscopy: IR spectra of pravastatin sodium were recorded using FTIR (Varian Cary 640 IR) with diffuse reflectance principle. Sample was prepared by trituriating with potassium bromide (KBr) in glass mortar and placing in the sample holder. The spectrum was scanned over a frequency range of 400 – 4000 cm⁻¹.

c) Melting point determination: Capillary method was used to record melting point.

2.3 Formulation of transdermal patches:

Formulation of transdermal patches of pravastatin sodium was carried out using polymers HPMC K15M, Guar gum and Eudragit RL100. PEG 400 and glycerine were used as plasticizer. (Prabhakara et al.,2010 ; Kooriyattil et al.,2013; Jagdale et al.,2013; Rowe et al.,2006)

**Formulation of Non medicated Patch**

The variables used while formulating the patch were concentration of polymer and plasticizer. (Table 1) Concentration of HPMC K15M was varied from 25mg to 100mg. Concentration of Guar gum was varied from 50mg to 150mg. The concentration for patch prepared from HPMC K15M and Eudragit RL100 was varied from 50+50mg to 50+150mg. The concentration of plasticizer was finalized differently for the polymers based on the plasticity of the film. It was varied from 0.1% to 0.2% for both plasticizer (PEG 400 and glycerine).

**Table 1 Formulation of non-medicated patch**

<table>
<thead>
<tr>
<th>Batch Code</th>
<th>HPMC K15M (mg)</th>
<th>Guar gum (mg)</th>
<th>HPMCK15M+ Eudragit RL100 (mg)</th>
<th>PEG 400 (ml)</th>
<th>Glycerine (ml)</th>
<th>Water (ml)</th>
<th>Acetone (ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>H1</td>
<td>25</td>
<td>-</td>
<td>-</td>
<td>0.1</td>
<td>-</td>
<td>5</td>
<td>-</td>
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<tr>
<td>H2</td>
<td>50</td>
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<td>-</td>
<td>0.1</td>
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<td>-</td>
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<td>-</td>
<td>-</td>
<td>0.2</td>
<td>-</td>
<td>5</td>
<td>-</td>
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<tr>
<td>H4</td>
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<td>-</td>
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<td>0.3</td>
<td>-</td>
<td>5</td>
<td>-</td>
</tr>
<tr>
<td>G1</td>
<td>-</td>
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<td>-</td>
<td>0.2</td>
<td>-</td>
<td>5</td>
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<tr>
<td>G2</td>
<td>-</td>
<td>50</td>
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<td>-</td>
</tr>
<tr>
<td>G3</td>
<td>-</td>
<td>50</td>
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<td>-</td>
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<td>-</td>
<td>0.1</td>
<td>5</td>
<td>-</td>
</tr>
<tr>
<td>E1</td>
<td>-</td>
<td>50+50</td>
<td>-</td>
<td>0.2</td>
<td>-</td>
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<td>2.5</td>
</tr>
<tr>
<td>E2</td>
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<td>100+50</td>
<td>-</td>
<td>0.2</td>
<td>-</td>
<td>2.5</td>
<td>2.5</td>
</tr>
<tr>
<td>E3</td>
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<td>50+100</td>
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<td>0.2</td>
<td>-</td>
<td>2.5</td>
<td>2.5</td>
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<tr>
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<td>-</td>
<td>2.5</td>
<td>2.5</td>
</tr>
</tbody>
</table>

For preparation of the transdermal patch solvent casting method was used. HPMC K15M and guar gum were mix with plasticizer in the concentration as mention in table 1 until a clear solution was obtained. This was then poured in a mould and allowed to dry in an oven maintained at 60°C till a
flexible film was formed. The dried patches were carefully removed from the mould, checked for any imperfections or air bubbles and cut into pieces squares of 1cm x 1cm. The samples were pack in aluminum foil and stored in desiccator maintained at room temperature. This condition maintained the integrity and elasticity of the patches. Few patches showed problem in formation of film, drying and flexibility. On this basis, concentrations of polymers and plasticizer were optimized.

**Formulation drug loaded transdermal patches**

For the medicated patches, calculated amount of drug was incorporated in polymeric solution before addition of plasticizer and casting was performed in the same way as mentioned above section. The formulation of patches is shown in table 2.

**Table 2** Formulation of drug loaded batches

<table>
<thead>
<tr>
<th>Batch code</th>
<th>Drug (mg)</th>
<th>HPMC K15M (mg)</th>
<th>Guar gum (mg)</th>
<th>HPMCK15M+ Eudragit (mg)</th>
<th>PEG 400 (ml)</th>
<th>Glycerine (ml)</th>
<th>Water (ml)</th>
<th>Acetone (ml)</th>
</tr>
</thead>
<tbody>
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<td>H3</td>
<td>90</td>
<td>50</td>
<td>-</td>
<td>-</td>
<td>0.3</td>
<td>-</td>
<td>5</td>
<td>-</td>
</tr>
<tr>
<td>H4</td>
<td>90</td>
<td>100</td>
<td>-</td>
<td>-</td>
<td>0.2</td>
<td>-</td>
<td>5</td>
<td>-</td>
</tr>
<tr>
<td>G3</td>
<td>90</td>
<td>-</td>
<td>50</td>
<td>-</td>
<td>-</td>
<td>0.1</td>
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<td>-</td>
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<tr>
<td>G6</td>
<td>90</td>
<td>-</td>
<td>100</td>
<td>-</td>
<td>-</td>
<td>0.2</td>
<td>5</td>
<td>-</td>
</tr>
<tr>
<td>E1</td>
<td>90</td>
<td>-</td>
<td>-</td>
<td>50+50</td>
<td>0.2</td>
<td>-</td>
<td>2.5</td>
<td>2.5</td>
</tr>
<tr>
<td>E3</td>
<td>90</td>
<td>-</td>
<td>-</td>
<td>50+100</td>
<td>0.2</td>
<td>-</td>
<td>2.5</td>
<td>2.5</td>
</tr>
<tr>
<td>E4</td>
<td>90</td>
<td>-</td>
<td>-</td>
<td>50+150</td>
<td>0.2</td>
<td>-</td>
<td>2.5</td>
<td>2.5</td>
</tr>
</tbody>
</table>

**Preparation of HPMC K15M + Eudragit RL100 patch:**

HPMC K15M+Eudragit RL100 patches were prepared by solvent evaporation technique. HPMCK15M and Eudragit RL100 were separately dissolved in distilled water and acetone respectively. These solutions were mix together continuously after addition of PEG 400. A prepared solution was poured into the mould. Patches were allowed to dry in preheated hot air oven at 60°C for 24hr. After drying patches were wrap into aluminum foil and kept into desiccators. The formulation of patches is shown in table 2

2.4 Evaluation of drug loaded transdermal patches (Sahu et al.,2012; Jayaprakash and Halith, 2010; Aqil and Asgar,2002)

**Physical appearance:** were visually inspected for color, clarity, flexibility and smoothness.

**Thickness of the film:** was determined at three different points using screw gauge.

**Weight variation:** was studied for ten randomly selected patches.

**Folding endurance test:** Folding endurance test was carried out by folding three patches at the same point a number of times till it broke.

**Flatness:** Three longitudinal strips were cut out from each film: one from the centre, one from the left side, and one from the right side. The length of each strip was measured and the variation in
length because of non-uniformity in flatness was measured by determining % constriction, with 0% constriction equivalent to 100% flatness.

Percent flatness (%) = \frac{L_1 - L_2}{L_2} \times 100 \hspace{1cm} \text{Formula 1}

Where,
- \( L_1 \) - Initial length of strip
- \( L_2 \) - Final length of strip

Swelling index: The patches of 1 cm² was weighed and put in a petridish containing 10 ml of double distilled water and were allowed to imbibe. Increase in weight of the patch was determined until a constant weight was observed. The degree of swelling (%S) was calculated using the formula

\[ S(\%) = \frac{W_t - W_0}{W_0} \times 100 \hspace{1cm} \text{Formula 2} \]

where,
- \( S \): percent swelling
- \( W_t \): weight of patch at time t
- \( W_0 \): weight of patch at time zero

Surface pH: For determination of surface pH the patches were left to swell for 2 h on the surface of agar plate, which was prepared by dissolving 2% (w/v) agar in warmed phosphate buffer saline solution (pH 7.4) under stirring and then pouring the solution into the petridish till gelling at room temperature. The surface pH was measured by means of pH paper placed on the surface of swollen patches.

Drug content of films: The patches (1cm²) were cut and added to a beaker containing 100 ml of phosphate buffered saline solution of pH 7.4. The medium was stirred with magnetic bead. The contents were filtered using Whatmann filter paper and the filtrate was examined for the drug content against the reference solution consisting of placebo films (contains no drug) at 239nm spectrophotometrically. The experiment was repeated in triplicate to validate the result.

% Moisture absorption: Accurately weighed films of each formulation were kept in desiccator which was maintained at 79.5% relative humidity (saturated solution of aluminum chloride) at room temperature and weighed after 3 days. The percentage moisture uptake was calculated as the difference between final and initial weight with respect to initial weight.

\[ \% \text{ Moisture absorption} = \frac{\text{Final weight} - \text{Initial weight}}{\text{Initial weight}} \times 100 \hspace{1cm} \text{Formula 3} \]

% Moisture Loss: Accurately weighed films of each formulation were kept in a desiccator and exposed to an atmosphere of 98% relative humidity (containing anhydrous calcium chloride) at room temperature and weighed after 3 days. The test was carried out in triplicate. The percentage moisture loss was calculated as the difference between initial and final weight with respect to initial weight.

In-vitro permeation studies using cellophane membrane:

In-vitro permeation studies were performed through cellophane membrane (Analab fine chemicals, specification: average flat width 22.54mm, average diameter 14.3mm, mol. wt. cut off approx.8000, pore size 2.4nm) by using Keshary- Chein diffusion cell with a receptor compartment capacity of 25 ml. The phosphate buffer saline solution (PBS) pH 7.4 was filled in the receptor compartment. The receptor solution was constantly and continuously stirred at 60 rpm using magnetic beads and was maintained at 32 ± 0.5°C temperature by circulating water through outer jacket of the diffusion cells. The formulated patches were placed over the membrane facing the matrix side in contact with the cellophane membrane. Aluminum foil was placed on upward side of patch to avoid moisture absorption from the surrounding. It was then mounted in the donor compartment, so that the membrane facing towards the receiver compartment. After mounting, 3ml of the sample was withdrawn at periodical time intervals of 1hr and equal volume of fresh buffer was replaced. The concentration of pravastatin sodium was determined by spectrophotometrically at 239 nm.
**In-vitro permeation studies using egg membrane**
Egg membrane was prepared by soaking the egg in the 0.1N HCl overnight and membrane was removed on second day as outer cover of egg get completely dissolve in the 0.1N HCL. Inner liquid of egg was removing after washing the membrane and then use for the permeation study of the transdermal patches. Mounting of formulation and determination of drug content in the withdrawn sample was carried out as mention above for the permeation study of drug through the cellophane membrane.

**Ex-vivo permeation studies using pig skin**
**Skin Preparation:**
Pig skin was brought from the slaughter house. The subcutaneous fat, tissue, blood vessel and epidermal hairs were carefully removed. Thickness of skin was measured using venire caliper which is found to be 1.4 mm. The skin with free of obvious holes or defects were cleaned with normal saline and finally with sterile water. Then it was soaked in phosphate buffer pH 7.4 solutions for 24 hrs refrigeration before use. To perform ex-vivo skin permeation, the skin was thawed at room temp and then used. Mounting of patch and determination of drug content in the withdrawn sample was carried out as mention above for the permeation study of drug through cellophane membrane.

**In-vitro Dissolution studies**
The prepared patches were subjected to in-vitro drug release to observe the kinetics of drug release from the formulations. The Transdermal patches were glued to the surface of watch glass using standard glue. The assembly was placed at the bottom of dissolution basket with the paddle speed of 50 rpm. 5ml of the sample was withdrawn from the bottom of the dissolution vessel containing 900 ml of phosphate buffer, pH 7.4 at 32°C ± 0.5°C. The amounts of drug release from the patches at different time intervals were determined by measuring the absorbance spectrophotometrically at 239nm.

**Permeation Data Analysis**
The flux (mcg cm⁻² hr⁻¹) (Jss) of drug was calculated from the slope of the plot of the cumulative amount of drug permeated per cm² of skin at steady state against the time using linear regression analysis:

\[ J_{ss} = \frac{(dq/dt) ss \times 1/A}{A} \]  
Where,  
(dq/dt) ss = steady state slope  
A = effective diffusion area

PCP disso v3 software was used for calculation of flux of pravastatin sodium.

**Kinetic analysis**
The rate and the mechanism of drug release were calculated by fitting the in-vitro, ex-vivo permeation and in-vitro dissolution data in using PCP Disso Version 2.08 software.

Zero-order equation, \[ Q = Q_0 k_0 t \]  
Where, \( Q \) is the amount of drug released at time \( t \), and \( k_0 \) is the release rate.

First order equation, \[ \ln Q = \ln Q_0 k_1 t \]  
Where, \( k_1 \) is the release rate constant

Higuchi’s equation, \[ Q = k_0 t^{1/2} \]
Where, Q is the amount of the drug released at time t and k₂ is the diffusion rate constant.

**Stability study:**
The formulation was stored at 40°C ± 2°C/75% ± 5% RH and 30°C ± 2°C/65% ± 5% RH test conditions in stability chambers (Thermolab) for 3 months. After study patch was evaluated for weight variation, thickness, surface pH and drug content.

### 3. Results and Discussion

#### 3.1 Characterization of pravastatin sodium

**UV Spectroscopic Studies**
The equation for line curve obtained was $y = 0.046x - 0.0027$ with correlation coefficient 0.9996 indicated extremely good linearity. Beer’s law was obeyed in the concentration range of 2-18 µg/ml. The percentage recovery of pravastatin sodium was found to be 95.95%±1.56 with % relative standard deviation (RSD) of 1.62%, indicating that there was no interference by the excipients in the method and the method is accurate.

The standard deviation and relative standard deviation (RSD) were ±0.1311 and 1.28% for intra-day test and ±0.152252 and 1.538% for inter-day precision test.

LOD was 0.586µg/ml, whereas LOQ was 1.95µg/ml. UV method was found to be simple, sensitive, accurate, precise and reproducible and can be used for the determination of pravastatin sodium in PBS of pH 7.4.

**FTIR Spectral Studies**

Fig. 1 showed FTIR spectrum of pure pravastatin sodium. This spectrum was compared with standard spectrum according to Japanese pharmacopeia. It was found that presented characteristic
peaks for specific structural group at 2878 cm$^{-1}$ (O-H, C-H carboxylic acid stretching), 3018 cm$^{-1}$ (aromatic C-H stretching), 1728 cm$^{-1}$ (carbonyl stretching), 1573, 1415 cm$^{-1}$ (-C= C aromatic, aromatic ring) also a very broad peak at 3540-3269 cm$^{-1}$ shows presence of ethanoic acid. The spectrum matches with standard.

The spectra for drug with polymer and patches have shown major peaks as that of pure drug indicating that there is no chemical interaction between drug and polymer as indicated in Fig. 2, 3 and 4.

![Fig. 2. FT-IR Spectroscopic study of optimized batch(G6) formulation.](image)

![Fig. 3. FT-IR Spectroscopic study of optimized batch (H3) formulation.](image)
Melting point determination
The melting point of pure pravastatin sodium was found to be in the range of 325-327°C. It is the temperature at which the solid phase exists in equilibrium with its liquid phases.

3.2 Formulation of transdermal patches

Formulation of Non medicated Patch

HPMC: Formulation containing higher concentration of polymer required proportionally higher concentration of plasticizer to form uniform patches without breaking. H3 and H4 produces patches having good plasticity and uniformity hence was selected for formation drug loaded transdermal patches (Table 2) (Gavali and Gaikwad,2010; Chandak and, Verma, 2009).

Guar gum: Formulation G1 and G2 containing same concentration of guar gum revealed that addition of PEG 400 at different concentration cause breaking of the solution. Patch obtained after drying showed breaking, less plasticity and difficulty in removing from the mould. Patch containing lower concentration of polymer and higher concentration of glycerin cause leakage of plasticizer while patch containing higher concentration of polymer and lower concentration of plasticizer didn't produce patch of good plasticity and breaking of patch observed. Therefore concentration of glycerin was increase proportionally. (Table 2) G7 produced solution of high consistency which was difficult to pour into the mould and patch obtained after drying shows shrinking of patch. G3 and G6 produce patches shown good plasticity and easily remove from mould and hence drug was loaded in G3 and G6 transdermal patches (Table 2). (Bhavya et al.,2012)

Eudragit RL100 + HPMC K15M:
To study the effect of hydrophobic polymer (Eudragit RL100) on the drug release, combination of Eudragit RL100 and HPMC K15M were tried using different concentration (Table 2). It was observed that addition of drug to the polymeric solution increases consistency of solution which is
difficult to pour into the mould. It was also observed that this effect was increase as concentration of Eudragit RL100 increase. Formulation containing higher concentration of HPMC K15M with Eudragit RL100 (E4) shows shrinkage of patch after drying. It was observed that addition of 0.2ml of PEG 400 produces patch having good plasticity. Formulation E1 and E3 were selected for formation drug loaded transdermal patches (Table 2).

Formulation H3, H4, G3, G6, E1, E3 (Table 2) produces patches with good uniformity, smoothness and plasticity which was selected and evaluated for further all study. (Gannu et al., 2007)

**Evaluation of pravastatin sodium transdermal patches:**

**Physical appearance:** It was observed that all patches appeared smooth and shows good flexibility and plasticity.

**Weight variation:** Values for weight variation range from 16.39±1.56 mg to 37.70±0.801 mg.

**Thickness of the film:** Variation in the thickness ranges from 0.31±0.011mm to 0.50±0.0182 mm.

**Folding endurance test:** The folding endurance was measured to ensure the ability of patch to withstand the rupture. Patches obtain from every formulation contain the required concentration of plasticizer which prevents easily breaking of the film. Values for folding endurance were varied in between 252±1.69 to 358±1.247.

It was revealed that formulation containing guar gum as natural polymer exhibit less mechanical strength as compare to HPMC K15M and Eudragit RL100 which are synthetic polymers. It has also shown that the formulation containing higher concentration of polymer exhibit more mechanical strength than formulation containing lower concentration.

**Flatness:** Prior optimization of aluminium mould helps to obtain transdermal patches having 100% flatness for every batch of different polymers.

**Swelling index:** The drug release from controlled release matrix gets affected by hydration of polymers. The consequence of water uptake could be the formation of empty spaces within the patch that could make its structure less resistant to mechanical stresses. Patches prepared from the hydrophilic polymer exhibits more swelling than the patches obtain from the lipophilic polymer. Natural hydrophilic polymer (guar gum) exhibits more swelling (32.21%) as compare to synthetic hydrophilic polymer (HPMC K15M) (19.40%). It was observed that patch containing higher concentration of guar gum exhibits more swelling. (Jagdale et al., 2012)

Eudragit RL100+HPMC K15M showed less swelling due to less absorption of water which may be due to lipophilic nature and insolubility of Eudragit RL100. Study showed that patch containing higher amount of Eudragit RL100 exhibit less (11.93%) swelling as compare to patch containing lower amount (14.88%).

**Surface pH:** The surface pH of the polymeric patches ranged between 6 to 7 which falls within the pH range of skin i.e. 4.0-6.5 which shows patches doesn’t exhibit irritation properties

**Drug content of films:** The values for drug content in different formulation ranges from 84.98±1.70 % to 94.0±1.38% which shows that drug get uniformly distributed within the patch.
% Moisture absorption (% MA): Low moisture absorption protects the material from microbial contamination and bulkiness of the patches. Formulation containing hydrophilic polymer absorbs more moisture (ranges from 2.54 - 6.60%) as compared to the patches containing hydrophobic polymers (ranges from 1.57-2.0 %). It was seen that the order of moisture absorption is guar gum > HPMC K15M > Eudragit RL100+HPMC K15M.

It was seen that patch containing higher concentration of Eudragit RL100 exhibits less moisture absorption which prevent microbial contamination of the patch.

% Moisture loss (% ML):
The small moisture loss in the formulation helps the film to remain stable, brittle and free from complete drying. Patches prepared from hydrophilic polymer exhibits more (ranges from 14.03-28.74%) moisture loss due to presence of more moisture content than the patch prepared from hydrophobic polymer (ranges from 9.98-10.23%).

Study showed that patch prepared using HPMC K15M+ Eudragit RL100 exhibits less moisture loss (ranges from 1.57±1.32-2.0±1.45) which revealed that presence of hydrophobic polymer maintain the moisture content of the patch and prevent brittleness and complete drying of the patches which help to maintain the stability of patches. It was also seen that moisture loss get decrease as the concentration of the Eudragit RL100 increases.

In-vitro permeation studies:
Using cellophane membrane:

![Fig. 5. In-vitro permeation study using cellophane membrane](image)

Cumulative % drug permeation data of different formulation through the cellophane membrane ranges from 62.46±1.90% to 89.35±1.67%. It was observed (Fig.5) that patch obtain from
hydrophilic polymers (H3, H4, G3, G6) exhibits more swelling and releases drug in the range of 73.16 ±1.73 - 89.35±1.67 % while patch containing combination of HPMC K15M+ Eudragit RL100 (E1,E3) releases drug in the range of 62.46±1.9 - 64.98±1.84 %. Eudragit RL100 retards drug release from the patches and retardation effect get increase as the concentration of Eudragit RL100 increases.

**Using egg membrane:**
Fig.6 indicated that all formulation had shown drug permeation in the range of 64.72±1.57 to 91.57±1.98%.

**Ex-vivo permeation studies using pig skin**
The ex-vivo release profile is an important tool that predicts how a drug will behave *in-vivo*.

Use of pig skin exhibits slightly decrease % cumulative drug permeation as that from the cellophane membrane, egg membrane and it ranges from 62.15±1.93% to 87.01±1.94% (Fig. 7)

The decrease in the drug release may be due to the difference in the membrane structure of the pig skin. The presence of hair follicle and chemical component retard the drug release through the pig skin as compare to the egg and cellophane membrane.
Study of flux (mcg/cm²/min):
The cumulative amount of drug permeated through a membrane is known as the flux of that drug. The values for the flux through different membrane used (cellophane, egg, pig skin) of different formulation were calculated using PCP disso v3 software. It was seen that egg membrane produces more flux (ranges from 470.9 ±1.67-686.8±1.54 mcg/cm²/min) as compare to the cellophane (454.78±1.54-665.97±1.67 mcg/cm²/min) and pig membrane (434.66± 1.86-652.6±1.67 mcg/cm²/min).

It was observed that presence of structural difference in the membranes used affect the values of flux produce and it was less for pig skin. It can be concluded that the formulation containing hydrophilic polymer (HPMC K15M, Guar gum) exhibits more swelling and produces more average flux which increases drug release from patch as compare to formulation containing HPMC K15M+Eudragit RL100.

In-vitro dissolution study:
In-vitro dissolution study revealed that all patches have shown maximum burst release as compare to permeation study within 8hrs. Patch prepared from higher concentration of guar gum exhibits maximum drug release i.e .73.66±1.89 (Fig.8) which occur because of formation of loose channels within polymeric matrix. Due to high hydrophilicity of Guar gum and HPMC K15M it absorbs water and dissolution of aqueous soluble fraction of polymer matrix leads to the swelling of polymer resulting into more release of drug from gelaneous pores of the films because of adequate porosity & diffusivity. The formation of such pores leads to decrease the mean diffusion path length of the drug molecules to release into the diffusion medium & hence, cause higher release rate.

Study showed that presence of hydrophobic polymer retards the drug release due to less solubility of polymeric matrix in the dissolution media. Eudragit RL100 attributed to the relatively
hydrophobic nature of polymer which was having less affinity for water, results in decrease in thermodynamic activity of the drug in the film & decreased drug release.

![Graph showing % Cumulative drug release over time](image)

**Fig. 8. In-vitro dissolution study**

**Release kinetic study:**
Formulation containing HPMC K15M followed zero order kinetic which shows that rate of drug release remains constant. Guar gum and HPMC K15M+Eudragit RL100 patches followed matrix type diffusion which shows that drug release take place by the diffusion mechanism and slow release was obtained.

**Stability study:** Stability study was carried for optimized batch G6. From the stability studies it was observed that there was no significant change on evaluation parameters before and after the study.

### 4. Conclusion

Patches were formulated using polymers HPMC K15M, guar gum and HPMC K15M+Eudragit RL100. Patches were found to have good physical appearance, folding endurance and flatness. FTIR data indicated that there were no interactions between drug and polymers used for preparation of patch. Patch containing higher concentration of HPMC K15M shows more sustained drug release due to less swelling than the patch containing lower concentration. Patch prepared using higher concentration of guar gum exhibits more and controlled drug release than patch due to more swelling of patch. Formulation G6 i.e guar gum 100 mg was selected as optimized batch. Optimized batch was found to be stable. Transdermal drug delivery can be potential drug delivery for the pravastatin sodium.
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References


