DEVELOPMENT AND EVALUATION OF TRANSDERMAL FILMS LOADED WITH PROPRANOLOL

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ABSTRACT
The aim of the present study is to prepare and evaluate transdermal films of propranolol (PL) by using sodium alginate (SA) & xanthan gum (XG) as biopolymer to prevent adverse effects related to oral administration. Transdermal films were prepared by solvent casting method by varying ratios of different blends of PL with sodium alginate and xanthan gum SA/XG. The compatibility studies have been carried out between drugs and polymers by using FTIR (Fourier transform infrared radiation) & differential scanning calorimetry (DSC) to determine any interactions between the drugs and the polymers. Films containing drugs were evaluated for the physicochemical properties such as weight uniformity, thickness, folding endurance, % moisture absorption studies, drug content uniformity, physical appearance, tensile strength and in vitro diffusion studies were carried out by Franz diffusion cell. In vitro permeation through skin of optimized formulation was compared with conventional gel of PL. various formulated patches were tested for their efficiency to cause skin irritation in rats. Smooth, thin, flexible & transparent film of PL were prepared by various concentration blends of sodium alginate & xanthan gum SA/XG. The compatibility studies were carried out through the FTIR & DSC which shows that there was no interaction between the drug and polymer hence they are compatible with polymers. Physicochemical properties such as weight uniformity, thickness, folding endurance, % moisture absorption studies, drug content uniformity, physical appearance, tensile strength were found to be uniform and reproducible. The in vitro diffusion studies is compared with the conventional gel which shows optimized formulation (A3) have better efficiency than the conventional gel formulation. The highest flux & diffusion ratio was found better in (A3) formulation it was about 0.266±0.043 mg/cm²/h & 8.39 mg/cm²/h hence better therapeutic effect was found in the A3 formulation therefore it is considered as optimized formulation. The skin irritation test was carried out in animals hence the optimized formulation did not show any kind of irritation and was found to stable and safe. By the above studies we can conclude that transdermal films of PL which were prepared by using biopolymers are effective vehicles for better transdermal delivery of PL to provide effective therapeutic response.

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INTRODUCTION

Drug delivery systems are developed to deliver the pharmaceutical active ingredients to systemic circulation from the various routes of administration. In recent years delivery of drugs through the transdermal route is gaining more attention because of its feasibility and better patient compliance & ease of administration. In response to this new idea transdermal drug delivery is developing rapidly by targeting the delivery of drug compounds to systemic circulation by topical application to the skin surface [1]. Transdermal drug delivery systems are adhesive systems with specific surface area which delivers the specified amount drug substance from the surface of intact skin to the systemic circulation at pre-determined rate or pre-programmed rate. These system delivers the drug systemically for extended period of time sustainably for specific period of time [2]. Now a days to avoid adverse effects caused due to the synthetic compounds various natural polymers are used. Various pharmaceutically accepted biopolymers such as xanthan gum, karaya gum, modified starch & agars have been used over synthetic and semisynthetic polymers in transdermal formulations. Compared to synthetic and semisynthetic polymers natural mucilages are more cheaper and safe, non-toxic, non-irritating in nature [3]. Transdermal film with varied concentrations of various natural polymer were prepared by using pharmaceutically accepted biopolymers such as xanthan gum and sodium alginate (SA/XA) in combination in different concentrations containing drug propranolol (PL) and permeation enhancer methanol these prepared films of propranolol(PL) were compared with the conventional gel. The main purpose of these films was to provide drug delivery by transdermal route and to deliver the specific amount of drug at controlled rate in systemic circulation to achieve therapeutic effectiveness for longer duration of time from transdermal film [4]. Drug release from the matrices is dependent on the polymer hydration & the rate of drug release from polymer carrier can be altered by the polymer-blends ratio and drug concentration [5].

The effect of hydrophilic plasticizer glycerin on physicochemical properties of xanthan gum and sodium alginate (XG/SG) films were evaluated and analyzed propranolol (PL) is selective beta 1 - adrenoreceptor blocking agent used in prevention of heart diseases such as myocardial infraction, coronary heart diseases, angina pectoris, tachycardia and heart failure. Propranolol (PL) (RS)-1-(1-methylamino)-3-(1-naphthoxy)propan-2-ol salt used to treat various cardiovascular diseases and has half-life of 3-4 hrs which makes it suitable candidate for controlled and extended release and to maintain drug plasma concentration for long duration. By this multiple dosing can be prevented which results in better therapeutic response. Oral bioavailability of propranolol (PL) is about 26% so to enhance the bioavailability of the (PL) transdermal route is selected for delivery of the drug. It has been reported that propranolol absorption in the duodenum and jejunum is directly proportional to the dose availability [6]. The bioavailability of drugs depends on the ability of drug to penetrate through stratum corneum and enter the systemic circulation to achieve therapeutic effectiveness [7]. A drug with log P (lipid/water partition coefficient) of ≤ 2 considered as potential candidate for transdermal delivery [8]. It has been increased interest now a days for the use of permeation enhancer that could modify the permeation of drug through skin [9]. In present study we made an attempt using by using methanol as permeation enhancer as methanol is considered to have good penetration efficiency by acting as lipid disrupting agent that increases the fluidity of stratum corneum by formation of capillary channels [10]. The purpose of this study was to provide delivery of drug at controlled rate across the intact skin to achieve required therapeutic effectiveness.

MATERIALS & METHODS

Propranolol was a gift sample from Micro labs, Bangalore, India. Xanthan Gum, Sodium Alginate obtained from Sisco research laboratories, Mumbai and Glycerol, Menthol. Procured from SD Fine chemical Ltd, Bangalore. All the chemicals and reagents used were of analytical grade Distilled water was used in all the experiments.

Preparation of drug-loaded transdermal films

The Transdermal patches were prepared by using solution casting technique. The bottom of the mould was wrapped with aluminum foil which was used as backing membrane. The purpose was to provide the delivery of drug at a controlled rate across intact skin to achieve a therapeutically effective drug level for a longer duration of time from transdermal films. Drug containing films were prepared by solution casting method. In brief, the required amounts of a mixture of XG/SA (Table 1) were weighed and prepared polymeric solution using quantity sufficient water by using magnetic stirrer at 800 rpm, kept a mixture for 2h after stirring. Accurately weighed propranolol (2.5 mg/mm²) and menthol (3% w/w) was dissolved in ethanol (6ml) by stirring for 10 min. The above mixture mixed with different concentrations of glycerin (1–5% w/w) and prepared polymeric solutions for 30 min. Finally mixed soft mass was poured on to cleaned specially designed glass moulds with the plastic transparent sheet and kept in a vacuum drier until it is dried to get the dried membrane. The cast polymer films with different formulations were then peeled off covered with aluminum foils and stored in a desiccator until further study.

| Table 1. Formulation chart of propranolol transdermal films. |
|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|
| Formulation code | propranolol (%) | Xanthan gum (%) | Sodium alginate (%) | Glycerine (%) | Menthol (%) |
| A1 | 2.5 | 21.0 | 75.0 | 0.5 | 1.0 |
| A2 | 2.5 | 30.5 | 64.5 | 1.0 | 2.0 |
| A3 | 2.5 | 41.0 | 51.5 | 2.0 | 3.0 |
| A4 | 2.5 | 25.5 | 65.0 | 3.0 | 4.0 |
| A5 | 2.5 | 15.5 | 74.0 | 3.5 | 4.5 |
| A6 | 2.5 | 8.5 | 80.0 | 4.0 | 5.0 |
| A7 | 2.5 | 2.0 | 85.0 | 4.5 | 6.0 |
Preformulation studies
Determination of Melting Point & Solubility studies[11]

Melting point of drug sample was performed by using Thieles tube method. The solubility has been determined after shaking a saturated solution of the drug for 2 hrs at 250°C in water, methanol, ether, acetone and acetonitrile respectively by using spectrophotometer.

Determination of partition co-efficient[12]

The partition co-efficient study was performed using n-octanol as oil phase and phosphate buffer pH 7.4 as aqueous phase. The partition co-efficient of drug Ko/w was calculated using the following formula.

FTIR analysis:

FTIR spectra of the pure drug & optimized formulation were obtained by FTIR spectrophotometer (Jassco - 4100, Japan).

Differential scanning calorimetry (DSC):

All dynamic DSC studies were carried out using DuPont thermal analyzer with 2010 DSC Q 200, module. The instrument was calibrated using high purity indium metal as standard and the scans of the samples were recorded under nitrogen gas purge at a heating rate of 10°C/min.

Evaluation of the prepared film formulations:

The thickness of the dry films was measured using microprocessor coating thickness gauze Quint sonic, Mumbai, India). The dry films (2.5 cm x 2.5 cm) were cut and placed on a control plate and the thickness of the film was measured. Mechanical properties, such as tensile strength and percentage elongation at break of SA/XG blends were measured as per ASTM D 638 using Universal Testing Machine (UTM) H 50 K M, 50K N Hounsfield, UK. A minimum of three samples were tested for each formulation and the average values were recorded.

Moisture Absorption:

Films were placed on open 5mL glass vials containing 5.0 g silica gel beads and held in place with a screw lid having a 0.90cm diameter of test area (0.60cm²). The desiccators containing vials kept in chambers with 75% RH (saturated NaCl solution) and 95% RH (water) were kept at 37°C for 7 days. Moisture uptake by the films was measured by weighing the dried film at 100°C for 24 h.

Drug contents in films:

Accurately weighed films were randomly cut rectangular (2.5 cm²) were dissolved in 50mL phosphate buffer (pH 7.4) and sonicated in ultra sonicator for 30 min and diluted. The concentration of PL in the receptor phase was determined by HPLC method[13]. The HPLC system consists of HPLC - shimadzu (Tokyo, Japan) LC - 6A model fitted with a μ - bond pack C18 (4.6x250mm) column, flow rate of 1mL/min, mobile phase consisted of acetonitrile–water–triethylamine 18:81:1 (v/v) as mobile phase and pinacidil monohydrate as internal standard (IS). UV detection was at 289 nm and PL and the IS were detected at retention times of 1.5 and 2.6 min, respectively. The method is sensitive with a limit of quantification of 20 ng mL⁻¹ the calibration plot for PL linear in the concentration range 20 – 200 ng ml⁻¹ Within-batch and total accuracy of the method ranged between 99.71% and 101.61%, and within-batch and total precision, expressed as the coefficient of variation, was 0.20-2.13%. The method can be successfully used for analysis of PL.

In vitro Drug Diffusion Study [14]

Drug diffusion studies were carried out in an open glass diffusion tube. A specimen dimension of films (2.5 cm²) was fixed to the hydrated cellophane membrane at one end of the open glass tube and placed in the receptor compartment containing buffer solution. The assembly was placed on a magnetic stirrer and stirred at 100 rpm. The temperature of the system was maintained at 37°C ± 1°C. A known amount of receptor medium (buffer) was withdrawn at regular intervals of time and sink condition was maintained by replacing equal volume of fresh saline. The drug concentration samples was measured by HPLC.

Stability of the transdermal films and prepared PL gel[15]

Formulation A3 (2.5 cm²) and conventional gel were subjected for stability studies at 25 °C/60% RH, 30 °C/65% RH, 40 °C/75% RH for 90 days and the above formulations were evaluated for drug content periodically.

In vitro skin permeation studies:

In vitro skin permeation studies were performed on a Franz diffusion cell with an effective diffusion area of 2.5 cm2 and 16 ml of receiver chamber capacity using rat abdominal skin. The animal study protocol was reviewed and approved by the Animal Ethics Committee at the Department of Pharmaceutics, JSS College of Pharmacy, Mysuru, India. Male albino rats weighing 125 - 132 g were used to excise full thickness skin. Rats were anaesthetized by ether, then hair of abdominal skin was removed by using electric clipper. Special care was taken while removing hairs, not to destroy the stratum corneum. The cleaned skin was washed with distilled water and stored in the deep freezer at −21°C until further use. The skin was brought to room temperature and mounted between the donor and receiver compartment of the Franz diffusion cell, where the stratum corneum side faced the donor compartment and the
dermal side faced the receiver compartment. Initially the donor compartment was empty and the receiver chamber was filled with ethanolic phosphate-buffered saline (PBS) pH 7.4 (30:70% v/v). The receiver fluid was stirred with a magnetic rotor at a speed of 300 rpm, to maintain the hydrodynamics of receiver fluid and the temperature maintained at 32°C ± 1°C. All the ethanolic PBS was replaced every 30 minutes to stabilize the skin. It was found that the receiver fluid showed negligible absorbance after 5 h and beyond, indicating complete stabilization of the skin. After complete stabilization of the skin, 2.5 cm² of the optimized film was placed into each donor compartment and sealed with paraffin film to provide occlusive conditions. Samples (0.5mL) were withdrawn at regular intervals (0.5, 1, 2, 3, 4, 5, 6, 7, 8h), filtered through a 0.45 µm membrane filter. The volume of release media was maintained by adding equal volume of fresh media after every sampling. Concentration of the PL in the sample was measured by HPLC.

Permeation data analysis:
Results are given mean ± standard deviation (S.D). The cumulative amount of drug permeated through the skin (mg/cm2) was plotted as a function of time (t) for each formulation. Drug flux (permeation rate) at steady state (Jss) was calculated by dividing the slope of the linear portion of the graph by the area of the diffusion cell. The permeability coefficient (Kp) was calculated by dividing Jss by the initial concentration of the drug in the donor cell (Co).

\[ Kp = \frac{Jss}{Co} \]  

Enhancement ratio (Er) was calculated by dividing the flux of the respective formulation by the flux of the control formulation:

\[ Er = \frac{Jss\ of\ formulation}{Jss\ of\ control} \]  

The results were analyzed statistically using Student’s t - test and significance was determined at 95% confident limit (P < 0.05).

Skin Irritation Study[16]:

The patches were tested for their potential to cause skin irritation/sensitization in rats. The skin irritation test was carried out on male albino rats weighing 125 to 132g. The animals were kept under standard laboratory conditions, with temperature of 25°C ± 1°C and relative humidity of 60% ± 5%. The animals were housed in cages, 5 per cage, with free access to a standard laboratory diet. The rats were shaved carefully avoiding peripheral damage and the patch was applied onto the nude skin using an adhesive. The rats were divided into five groups. On the previous day of the experiment, the hair on the back side area of rat was removed. The animals of group I were served as normal without any treatment. One group of animals (Group II, control) was applied with marketed adhesive tape (official adhesive tape in USP). Transdermal systems (blank and drug loaded) were applied onto nude skin of animals of I and IV groups. A 0.8 % v/v aqueous solution of formalin was applied as a standard irritant (Group V). The animals were applied with new patch/formalin solution each day upto 7 days and finally the application sites were graded according to a scoring scale.

RESULTS AND DISCUSSION

FTIR Spectroscopy

![FTIR Spectra](image.png)

Figure 1. IR spectra of pure drug (A) and formulation (B).

Preformulation study Melting point of PL was found to be 121.1°C. PL is freely soluble in water (1000µg/ml), soluble in methanol (500µg/ml) and ether (495µg/ml), slightly soluble in acetone (1.1µg/ml) and acetonitrile (0.86µg/ml), practically insoluble in hexane (0.001µg/ml). The value of partition co-efficient (P) value of PL was experimentally found to be 0.753. The results obtained also indicate that the drug possesses sufficient lipophilicity, which fulfill the requirements of formulating the selected drug into a transdermal film. The biphasic nature of drug mimics the biphasic nature of skin, thus ensuring easy penetration through the skin. The FT-IR spectra and data of pure drug PL and Propranolol Tartrate with polymers are shown in the figure 1. The IR spectra of pure PL
and polymers was found to be identical. The characteristic IR absorption peaks of PL at 2932.24 cm\(^{-1}\) (C-H stretch), 1238.20 cm\(^{-1}\) (Aromatic ether), 1179.25 cm\(^{-1}\) (Isopropyl group), 1111.89 cm\(^{-1}\) (ether), 841.85 cm\(^{-1}\) (1,4-disubstituted benzene) were present. FTIR spectra of the drug with polymers showed all the PL characteristics absorption bands suggesting there is no chemical interactions between the drug and polymers used in the formulation. Compared the IR spectra and interpretation of this region in our spectra agrees with their conclusions [17].

**Differential Scanning Calorimetry (DSC):**

![DSC Thermogram](image)

**Figure 2: DSC Thermogram of pure drug and formulation.**

To understand the compatible state of the drug with polymers, DSC studies were carried out on pure drug and drug loaded patch, the thermo grams data obtained are shown in Figure 2. Propranolol exhibits a sharp endothermic peak at 164.074\(^\circ\)C. It was observed that presence of the endothermic peak at 166.193\(^\circ\)C in the drug loaded patches indicated, that the drug is distributed in the patch without any degradation and compatible with XG/SA. Compared the DSC data and interpretation of this region in our data agrees with their conclusions [18].

**Evaluation of Transdermal films:**

Seven film formulations (A1 - A7) of films were prepared using solution casting method and dried. Films consist of glycerine as a plasticizer and menthol as permeation enhancer. Surface of the film was smooth, with elegant appearance, good physical properties. Flatness of the films were observed better, when the amount of SA > 30% in the formulated films, might be SA having α-L-guloronic acid, which is interact with XG produces good flatness to the film [19]. Thus these formulations can maintain a smooth and uniform surface when applied on skin.

**Mechanical properties:**

Thickness of the prepared films was in the range of 0.25 to 0.27mm as shown in Table 2. Thickness, tensile strength and % elongation of the films increasing by increased ratio of XG and plasticizer in the films. Added glycerin alters the physical and mechanical properties by enhancing the mobility of polymers chains of SA, XG by hydrogen bonding [20]. However it was found that 2% of glycerin gives the best plasticizer effect for PL loaded film. The prepared films were evaluated for its uniformity of weight, tensile strength, percentage elongation, folding endurance, percentage moisture absorption, percentage moisture loss and drug content, the data was presented in Table 2.
Table 2: Evaluation studies of different formulations.

<table>
<thead>
<tr>
<th>Formulation</th>
<th>Thickness of film (mm) Mean ± S.D</th>
<th>% Elongation (mg/mm2) Mean ± S.D*</th>
<th>Folding endurance Mean ± SD*</th>
<th>% Moisture Absorption Mean ± S.D*</th>
<th>% Moisture Absorption Mean ± S.D*</th>
<th>Drug content (mg) Mean ± S.D*</th>
</tr>
</thead>
<tbody>
<tr>
<td>A1</td>
<td>0.25 ±0.006</td>
<td>2.58 ± 0.0036</td>
<td>20.13 ± 0.46</td>
<td>269.33 ±2.41</td>
<td>1.59 ± 0.13</td>
<td>2.29 ±0.14</td>
</tr>
<tr>
<td>A2</td>
<td>0.23 ±0.018</td>
<td>2.67 ± 0.0024</td>
<td>21.78 ± 0.12</td>
<td>277.50 ±1.00</td>
<td>1.57 ±0.34</td>
<td>2.39 ±0.15</td>
</tr>
<tr>
<td>A3</td>
<td>0.25 ±0.011</td>
<td>2.98 ± 0.0047</td>
<td>19.66 ± 0.18</td>
<td>272.32 ±3.07</td>
<td>1.60 ±0.22</td>
<td>2.45 ±0.08</td>
</tr>
<tr>
<td>A4</td>
<td>0.27 ±0.013</td>
<td>3.12 ± 0.0056</td>
<td>24.13 ± 0.22</td>
<td>267.35 ±4.77</td>
<td>1.64 ±0.44</td>
<td>2.38 ±0.16</td>
</tr>
<tr>
<td>A5</td>
<td>0.25 ±0.006</td>
<td>3.28 ± 0.0013</td>
<td>29.98 ± 0.21</td>
<td>280.00 ±1.00</td>
<td>1.68 ±0.24</td>
<td>2.36 ±0.14</td>
</tr>
<tr>
<td>A6</td>
<td>0.26 ±0.018</td>
<td>3.45 ± 0.0028</td>
<td>31.37 ± 0.15</td>
<td>266.00 ±5.20</td>
<td>1.72 ±0.17</td>
<td>2.34 ±0.15</td>
</tr>
<tr>
<td>A7</td>
<td>0.27 ±0.011</td>
<td>3.57 ± 0.0015</td>
<td>33.55 ± 0.16</td>
<td>269.33 ±5.00</td>
<td>1.73 ±0.18</td>
<td>2.320.14</td>
</tr>
</tbody>
</table>

i. Drug content analysis

![Drug Content Analysis](image1)

Figure 3: Graphical representation of drug content analysis.

ii. Surface morphological studies

![Surface Morphology](image2)

Figure 4: Surface morphology of Propranolol transdermal patch (A3).

All surface of the film was smooth, with elegant appearance, good physical properties. Flatness of the films was observed better when the amount of SA > 30% in the formulated films. Thus these formulations can maintain a smooth and uniform surface when applied on skin. The surface morphology of the film formulation A3 was observed using SEM as shown in Figure 4 which indicates that the formulated film has smooth surface.

In vitro Diffusion studies

From the diffusion studies, it was observed that, there was a significant diffusion of drug from propranolol films at gastric pH. At the end of 8th h, drug diffuses from formulation A3 (70.28%) was maximum than A1 (55.74%), A2 (58.24%), A4 (50.66%), A5 (56.88%), A6 (53.12%), and A7 (32.10%). It was clear that maximum amount of PL was diffuses from the formulation (A3). The data was shown in table 3 and the graphical representation was shown in figure 5. From the above results, it can be concluded that drug diffusion from the films was controlled due to increased amounts of XG showed higher swell ability of the film. Release of the drug
from transdermal patches is controlled by the chemical properties of the drug and delivery form, as well as physiological and physicochemical properties of the biological membrane. The process of drug release in most controlled release devices is governed by diffusion and the polymer matrix has strong influence on the diffusivity as the motion of a small molecule is restricted by the three dimensional network of polymer chains. The reason for high drug release from A3, because xanthan gum is hydrophilic nature, exhibits hydration and swelling of the patches. Xanthan Gum is known to have larger cavity size in its polymeric network and thus it may involve a faster mode of diffusion of propranolol from the formulations A3 as compared to other formulations leading to higher skin permeation. The % of plasticizer from the film could reduce tortuosity of aqueous pore channels of the films, respectively [21]. In order to understand mechanism of drug release, in vitro release data were treated to kinetic models and linearity was observed with respect to Higuchi equation. The correlation coefficient obtained from Higuchi plot was found to be in the range of 0.9832 to 0.9924. This indicates that mechanism of drug release was diffusion type. As indicated by higher R² values, the drug release from all formulations follows first order release and Higuchi model. Since it was confirmed as Higuchi model, the diffusion mechanism was swelling and diffusion controlled.

Table 3: In-vitro drug release studies of different formulations.

<table>
<thead>
<tr>
<th>Time in hours</th>
<th>Percentage drug release of different formulations</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>A1</td>
</tr>
<tr>
<td>1</td>
<td>12.13</td>
</tr>
<tr>
<td>2</td>
<td>18.16</td>
</tr>
<tr>
<td>3</td>
<td>23.25</td>
</tr>
<tr>
<td>4</td>
<td>29.68</td>
</tr>
<tr>
<td>5</td>
<td>37.56</td>
</tr>
<tr>
<td>6</td>
<td>43.76</td>
</tr>
<tr>
<td>7</td>
<td>49.35</td>
</tr>
<tr>
<td>8</td>
<td>55.74</td>
</tr>
</tbody>
</table>

SD = Standard deviation

![Graphic](image.jpg)

**Figure 5: graphical representation of in vitro drug release studies.**

**Stability studies**

The optimized formulation A3 was subjected for stability studies and estimated drug content at the end of 60 days. However, no significance change in drug content from formulation A3 and conventional gel after the study period, indicating drug was stable.

**In vitro Skin permeation study**

In vitro skin permeation studies were performed to compare the release of drug from 7 different film formulations (A3 - A7) and conventional gel, all having PL. As expected the flux of PL from films was found significantly higher (P <0.05) than the flux of PL from conventional gel presented in Table 4. In vitro skin permeation was highest and lowest in formulation A3 and A7 respectively. The formulations F4 showed an intermediate skin permeation profile. Increasing the concentration (3 to 6% w/w) of
penetration enhancer showed a significant difference (P < 0.05) in the flux of PL. The highest flux and enhancement ratio for PL from the film (A3) was found to be 0.268 ± 0.011 mg/cm²/h & 8.37 mg/cm²/h respectively.

Table 4. Permeability Parameters of Different Formulations.

<table>
<thead>
<tr>
<th>Formulation</th>
<th>Menthol %</th>
<th>Jss ± SD (Mg/cm²/h)</th>
<th>Permeability coefficient (kp) ± SD</th>
<th>Er mg/cm²/h</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gel (control)</td>
<td>-</td>
<td>0.032 ± 0.032</td>
<td>0.013 ± 0.023</td>
<td>1.00</td>
</tr>
<tr>
<td>A1</td>
<td>1.0</td>
<td>0.159 ± 0.012</td>
<td>0.067 ± 0.014</td>
<td>2.15</td>
</tr>
<tr>
<td>A2</td>
<td>2.0</td>
<td>0.223 ± 0.041</td>
<td>0.069 ± 0.014</td>
<td>6.96</td>
</tr>
<tr>
<td>A3</td>
<td>3.0</td>
<td>0.268 ± 0.011</td>
<td>0.093 ± 0.031</td>
<td>6.37</td>
</tr>
<tr>
<td>A4</td>
<td>4.0</td>
<td>0.231 ± 0.056</td>
<td>0.109 ± 0.021</td>
<td>7.23</td>
</tr>
<tr>
<td>A5</td>
<td>5.0</td>
<td>0.199 ± 0.021</td>
<td>0.097 ± 0.014</td>
<td>6.21</td>
</tr>
<tr>
<td>A6</td>
<td>6.0</td>
<td>0.176 ± 0.011</td>
<td>0.084 ± 0.014</td>
<td>5.50</td>
</tr>
<tr>
<td>A7</td>
<td>7.0</td>
<td>0.157 ± 0.012</td>
<td>0.075 ± 0.014</td>
<td>4.90</td>
</tr>
</tbody>
</table>

*(N=3)*

Menthol is expected to be a moderate skin permeation enhancer. In contrast, menthol enhanced the skin permeation of the drug by increasing both the skin concentration and the diffusion rate in skin because menthol contains functional group of hydrogen bonding. Menthol is a lipophilic terpene found to be more effective because menthol found to enhance the penetration of drug by both lipid and pore pathway [22]. Increase in the concentration of penetration enhancer from 1% wt/wt to 3% w/w, resulted increases in the enhancement ratio and the flux. But even after increasing the penetration enhancer from 3.0 % to 6 % w/w and plasticizer from 3.0% to 4.5% w/w for formulation A4 and A7 showed decreased enhancement ratio. Because increased ratio of XG in the films showed higher swellability of the film, plasticizer leaches from the film could reduce tortuosity of aqueous pore channels of the films. So that delivery of drug at a controlled rate across intact skin to achieve a therapeutically effective drug level for a longer duration of time from transdermal films. When enhancement ratio <1.0 indicates that enhancer has no permeation enhancing activity.

Skin irritation test

Based on higher drug permeation, formulation A3 was selected for the skin irritation test. The skin irritation study indicated that neither the polymer nor the drug caused any noticeable irritation or inflammation on or around the patch area, either during the period of study or after removal of the patch.

CONCLUSION

On the basis of good mechanical properties, better compatibility and stability of drug with polymer, highest drug permeation, we selected film formulation A3 (3% Menthol) for use in skin irritation test. From the result it can be concluded that the developed film formulation A3 have great potential for transdermal drug delivery. Developed film formulation A3 has the best effective combination of polymer to achieve therapeutic plasma concentration. But further research should be recommended before the film formulations are used on humans.

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