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DEVELOPMENT AND EVALUATION OF TRANSDERMAL FILMS LOADED WITH ANTIHYPERTENSIVE DRUG

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ABSTRACT

Objective: The aim of the present study was to prepare and evaluate transdermal films of Metoprolol Tartrate (MT) using sodium alginate (SA) and xanthan gum (XG) as biopolymers to minimize adverse effects associated with oral administration. Methods: Transdermal films of MT with SA / XG by varying the blend ratios were prepared by solution casting method. FTIR and DSC were studied to assess any interaction between the drug and the polymers. Drug loaded films were evaluated for physicochemical characteristics such as physical appearance, thickness, weight uniformity, folding endurance, % moisture absorption studies, SEM analysis, drug content uniformity. Tensile strength, *invitro* diffusion was determined by Franz diffusion cell. *In vitro* skin permeation of optimized formulation was compared with that of MT conventional gel. The patches were tested for their potential to cause skin irritation in rats. Results: Thin, flexible, smooth and transparent films of MT were obtained with SA/XG blends. The FT-IR and DSC studies confirmed no interaction between the drug and polymers. SEM pictures clearly exhibited the homogeneous dispersion of MT in the transdermal films. Thickness, Tensile strength, folding endurance and % elongation were found to be uniform and reproducible. *In vitro* diffusion release studies revels effectiveness of optimized formulation when compared with the conventional gel. The highest flux and enhancement ratio for MT from the film (A3) was found to be 0.268 ± 0.041 mg/cm^2/h & 8.37 mg/cm^2/h respectively. The skin irritation study indicated that neither the polymer nor the drug caused any noticeable irritation. Conclusions: It could be concluded that the polymeric matrix-type transdermal films of biopolymer based transdermal films are potential vehicles for improved transdermal delivery of MT effective therapy.

KEYWORDS: Metoprolol Tartrate, Sodium alginate, Xanthan gum, Transdermal release Skin irritation test

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INTRODUCTION

Drug delivery systems are designed to support the passage of drug substances from the surface of the skin through its various layers and into the systemic circulation. In response to this new idea several transdermal drug delivery systems have recently been developed, aiming to achieve the objective of systemic medication through topical application to the intact skin surface[1]. Transdermal drug delivery systems are adhesive, drug containing devices of defined surface area that deliver a pre-determined amount of drug to the surface of intact skin at a pre-programmed rate. These systems provide drug systemically at a predictable rate and maintain the rate for extended periods of time[2]. Various natural substances xanthan gum,gum karaya, modified starch and agar have been used in the formulations of transdermal films. Mucilage of natural origin is preferred over semi-synthetic and synthetic substances because they are comparatively cheaper, abundantly available, non-irritating and non-toxic in nature[3].Transdermal films with varied ratios of pharmaceutically acceptable biopolymers Xanthan Gum (XG) & Sodium Alginate (SA) combination containing the drug Metoprolol Tartrate (MT) with permeation enhancer (menthol). The prepared films were compared with the prepared conventional gel. 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. Sodium alginate (SA) is a natural polymer is very promising and has been widely exploited in pharmaceutical industry, because of its tailor-made to suit the demands of applications[4]. Xanthan gum is a hydrophilic polymer, had been limited for use in thickening, suspending, and emulsifying water based systems. It is gaining appreciation for the fabrication of pharmaceuticals with uniform drug release characteristics. Drug release property of matrices is preceded by polymer hydration and the rate of drug release from polymer carrier can be tailor-made by selecting a suitable polymer-blends composition and drug concentration[5]. The effect of hydrophilic plasticizers such as glycerin on physicochemical properties on sodium alginate /xanthan gum (SA/XG) film was evaluated.

Metoprolol tartrate (MT) is a selective beta1-adrenoreceptor blocking agent. Metoprolol tartrate is (±)-1-(isopropylamino)-3-[p-(2-methoxyethyl) phenoxy]-2-propanol (2:1) dextro-tartrate salt used in Essential hypertension, prevention after a myocardial infarction,tachycardia, coronary heart disease (prevention of angina attacks), treatment of heart failure. The maintenance of a constant plasma level of a cardiovascular drug is important in ensuring the desired therapeutic response. Since the half-life of MT is ~3 to 4 hours,2 multiple doses are needed to maintain a constant plasma concentration for a good therapeutic response and improved patient compliance. It has also been reported that MT absorption in the duodenum and jejunum is directly proportional to the dose availability.Oral bioavailability of metoprolol tartrate is around 40 % [6].

Penetration depends on ability of drug to penetrate the stratum corneum, enter the systemic circulation and to achieve the therapeutic effect[7]. A drug with log P (lipid/water partition coefficient) of ≤ 2 considered as potential candidate for transdermal delivery[8]. There has been increased interest during recent years in the use of chemical enhancer that could modify drug permeation through skin. It is desirable to develop topical delivery systems that do not require the use of chemical enhancers to facilitate drug permeation through skin[9]. In the present study we made an attempt by using menthol as a penetration enhancer. Because menthol is considered to have good permeation enhancing agent by acting as a lipid disrupting agent that increases the fluidity

of stratum corneum lipid by increasing the formation of capillary channels[10]. Ttransdermal films with varied ratios nonirritating and pharmaceutically acceptable biopolymers SA and XG combination containing the drug MT with permeation. enhancer (menthol). The prepared films were compared with the marketed conventional gel. 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.

MATERALS & METHODS

Metoprolol Tartrate 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. Other chemicals and reagents 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 solvent casting technique. The bottom of the mould was wrapped with aluminum foil which was used as backing membrane. 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, kept aside for 2h after stirring. Accurately weighed Metoprolol Tartrate (2.5 mg/mm^2) 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 molds with the plastic transparent sheet and kept in a vacuum drier until 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 Metoprolol Tartrate transdermal films

Formulation code	Metoprolol Tartrate (%)	Xanthan Gum (%)	Sodium alginate (%)	Glycerin (%)	Menthol (%)
A 1	2.5	20.0	76.0	0.5	1.0
A 2	2.5	30.5	64.0	1.0	2.0
A 3	**2.5**	**40.5**	**51.0**	**2.0**	**3.0**
A 4	2.5	25.5	65.0	3.0	4.0
A 5	2.5	15.5	74.0	3.5	4.5
A 6	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 25^0 C in water, methanol, ether, acetone and acetonitrile, respectively.

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 $K_{o/w}$ was calculated using the following formula.

$$K_{o/w} = \frac{\text{Concentration in octanol}}{\text{Concentration in phosphate buffer pH 7.4}}$$

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 10^0C/ 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 (0.60cm^2). The desiccators containing vials kept in chambers with 75% RH (saturated NaCl solution) and 95% RH (water) were kept at 37^0C for 7 days. Moisture uptake by the films was measured by weighing the dried film at 100^0C for 24 h.

Drug contents in films

Accurately weighed films were randomly cut rectangular (2.5 cm^2) were dissolved in 50mL phosphate buffer (pH 7.4) and sonicated in ultra sonicator for 30 min and diluted. The concentration of MT 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 275 nm and MT 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 MT 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 MT.

Scanning electron microscopy

SEM studies are carried using JOEL JSM-T330A Scanning Electron Microscope. The external morphology of the formulation A3 was analyzed using a scanning electron microscope to determine the drug distribution in the film.

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 cm^2) 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 MT gel [15]

Formulation A3 (2.5 cm^2) and conventional gel were subjected for stability studies at 25 ºC/60% RH, 30 ºC/65% RH, 40 ºC/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 cm^2 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, Farooquias College of Pharmacy, Mysore, 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^oC 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 hydro dynamics of receiver fluid and the temperature maintained at 32 ^0C ± 1^0C. 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 cm^2 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-membrane filter. The volume of release media was maintained by adding equal volume of fresh media after every sampling, Concentration of the MT 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)

$Kp = Jss / Co$……. (2)

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

Er = Jss of formulation / Jss of control……. (3)

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 to132g. The animals were kept under standard laboratory conditions, with temperature of 25^0C ± 1^0C 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 III 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 always by the same investigator.

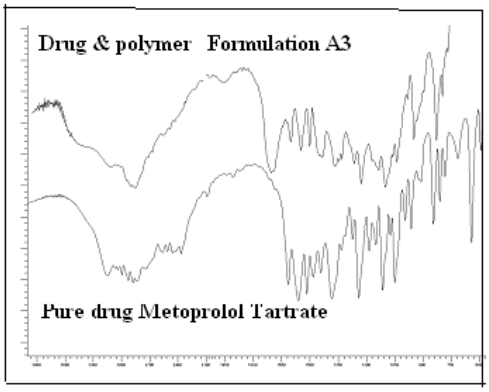
RESULT AND DISCUSSION

Pre formulation study

Melting point of MT was found to be 121.1^{o}C. MT is Freely soluble in water (1000µg/ml), soluble in methanol (500µg/ml) and ether (496µg/ml), slightly soluble in acetone (1.1µg/ml) and acetonitrile (0.89µg/ml), practically insoluble in hexane (0.001µg/ml). The value of partition co-efficient (P) value of MT 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.

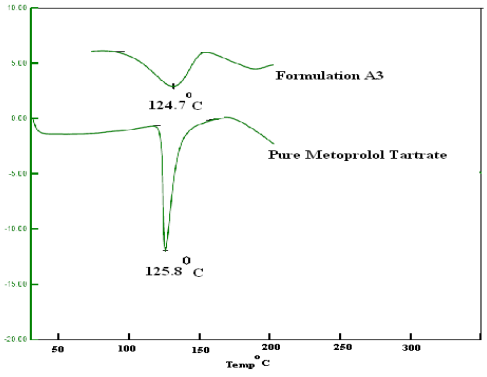
The FT-IR spectra and data of pure drug MT and Metoprolol Tartrate with polymers are shown in the figure 1. The IR spectra of pure MT and polymers was found to be identical. The characteristic IR absorption peaks of MT at 2934.24 cm^{-1} (C-H stretch), 1242.20 cm−1 (Aromatic ether), 1189.25 cm^{-1} (Isopropyl group), 1114.89 cm^{-1} (ether), 844.85 cm^{-1}(1,4-disubstituted benzene) were present. FTIR spectra of the drug with polymers showed all the MT 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].

Figure 1
FTIR spectra of Metoprolol



Tartrate & Metoprolol Tartrate with Polymers (Formulation A3)

Figure 2
DSC Thermogram of Metoprolol



Tartrate & Metoprolol Tartrate with polymers (Formulation A3)

Differential Scanning Calorimetry (DSC)

To understand the compatible state of the drug, DSC studies were carried out on pure drug and drug loaded patch, the thermo grams data obtained are shown in Figure 2. Metoprolol Tartrate exhibits a sharp endothermic peak at 125.8^{0}C. It was observed that presence of the endothermic peak at 124.7^{0}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 0.24 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 MT 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 presented in Table 2.

Table 2
Mechanical properties and Drug content of the prepared films

Formulation	Thickness of film (mm) Mean ± S.D*	Tensile Strength (kg/mm2) Mean ± S.D*	% Elongation (mg/mm2) Mean ± S.D*	Folding endurance Mean± SD*	% Moisture Absorption Mean ± S.D*	Drug content (mg) Mean ± S.D*
A1	0.25 ± 0.005	2.48 ± 0.0036	20.13 ± 0.45	267.33 ± 2.51	1.59 ± 0.12	2.29 ± 0.13
A2	0.23 ± 0.015	2.67 ± 0.0023	21.79 ± 0.12	276.50 ± 1.00	1.58 ± 0.32	2.39 ± 0.11
A3	0.24 ± 0.011	2.98 ± 0.0046	19.64 ± 0.19	272.33 ± 3.06	1.60 ± 0.21	2.45± 0.09
A4	0.27 ± 0.010	3.12 ± 0.0053	24.12 ± 0.21	267.33 ± 4.72	1.63 ± 0.42	2.38 ± 0.14
A5	0.25 ± 0.005	3.29 ± 0.0013	28.98 ± 0.21	270.00 ± 1.00	1.68 ± 0.23	2.36 ± 0.15
A6	0.26 ± 0.017	3.45 ± 0.0026	31.38 ± 0.11	265.00± 5.10	1.71 ± 0.12	2.34± 0.16
A7	0.27 ± 0.010	3.57 ± 0.0011	33.56 ± 0.19	265.33± 5.00	1.73 ± 0.16	2.32± 0.13

Standard deviation, n =3

Scanning Electron Microscopy (SEM)

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 3 which indicates that the formulated film has smooth surface.

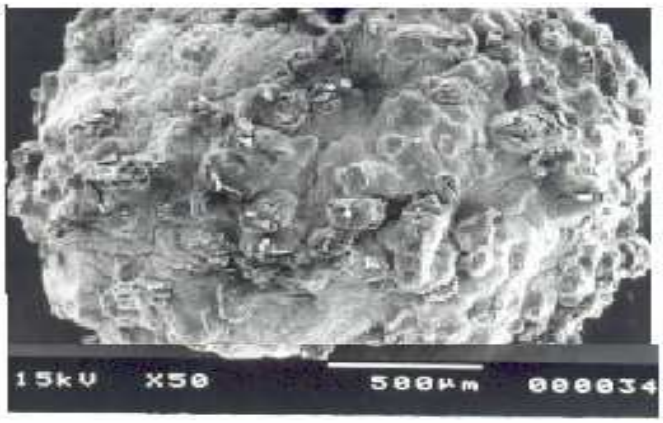


Figure 3
Scanning electron microscopy of Metaprolol Tartrate patch (A3)

In vitro Diffusion studies

From the diffusion studies, it was observed that, there was a significant diffusion of drug from Metaprolol Tartrate 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 MT was diffuses from the formulation (A3). From the above results, it can be concluded that drug diffusion from the films was controlled due to increased amounts of XG showed higher swellability 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 release drug 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 Metoprolol tartrate 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 R^2 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.

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 MT. As expected the flux of MT from films was found significantly higher ($P < 0.05$) than the flux of MT from conventional gel presented in Table 3. *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 MT. The highest flux and enhancement ratio for MT from the film (A3) was found to be 0.268 ± 0.041 mg/cm^2/h & 8.37 mg/cm^2/h respectively.

Table 3
Permeability Parameters of Different Formulations

Formulation	Menthol (%)	Jss ± SD * (mg/ cm^2/h)	Permeability coefficient (Kp) ± SD*	Er mg/cm^2/h
Gel (Control)	-	0.032 ± 0.032	0.013 ± 0.023	1.00
A1	1.0	0.159 ± 0.012	0.069 ± 0.014	2.15
A2	2.0	0.223 ± 0.041	0.093 ± 0.031	6.96
A3	3.0	0.268 ± 0.011	0.109 ± 0.021	8.37
A4	4.0	0.231 ± 0.056	0.097 ± 0.014	7.23
A5	4.5	0.199 ± 0.021	0.084 ± 0.014	6.21
A6	5.0	0.176 ± 0.011	0. 075 ± 0.014	5.50
A7	6.0	0.157 ± 0.012	0.067± 0.014	4.90

**** (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 lipophillic 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 % w/w to 6 % and plasticizer from 3.0% to 4.5% w/w in 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 compatability 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 experiments should be carried out before the film formulations are used on humans.

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