



Fabrication of Polymeric Film Forming Topical Gels

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ABSTRACT

The present work reports a topical formulation combining the advantages of polymeric films and gels for drug delivery. Film forming gels were formulated using cellulose polymers, the gel when applied over the skin form a continuous film releasing drug at a controlled speed. The concentrations of the cellulose polymers and humectants were varied and their effects on the physicochemical parameters of the gels were assessed. The gels were evaluated for pH, clarity, drying time, viscosity, drug content, spreadability, textural properties, *in-vitro* and *ex-vivo* drug diffusion profiles. The optimized formulations were further subjected to hot-plate and tail-flick tests in rats in order to assess the anti nociceptive potential of the local anaesthetic film forming gel. The optimized gel prepared with a polysaccharide polymer and ethanol as the solvent exhibited clarity, transparent and shiny, quick drying time. Films formed over the skin and were aesthetically appealing. The gels showed a high drug diffusion rate over the porcine ear membrane and a flux value of 211 $\mu\text{g/hr/cm}^2$. The anti-nociceptive activity showed that the film forming gels could significantly ($P \leq 0.05$) inhibit pain perception. Film forming gels of local anaesthetics have the potential to inhibit peripheral pain and hence may be considered as suitable delivery systems for pain management.

Keywords: Film forming gel, Topical drug Delivery, Local anaesthetic, Peripheral Neuropathic pain.

INTRODUCTION

Neuropathic pain is caused due to nerve damage or injury and is a commonly occurring complaint in patients. This condition may be precipitated by drugs, radiation therapy, surgery, infection and diseases like diabetes, HIV and cancer.¹ The symptoms of Neuropathic pain include burning, aching or itching with superimposed lancinating pains, tingling and severe allodynia.²

Local anaesthetics which are topically applied can play a role in blocking the nerve conduction by reversibly binding with the D4-S6 part of the α -subunit of the voltage-gated sodium channels in the nerve membrane.³ Topical lidocaine has been shown to reduce pain in patients with post-herpetic neuralgia and allodynia. Lidocaine patch 5% is the sole local anesthetic formulation that has been studied in detail and a number of clinical trials have been carried out to assess its efficacy for management of neuropathic pain s along with other oral formulations.^{4,5}

Local application of therapeutic compounds either to the skin, or into the systemic circulation after passage through the skin, offers many advantages over oral and injectable drug delivery. These potential advantages include avoidance of hepatic first-pass metabolism, improved patient compliance and ease of application to the skin. In case of local delivery directly by administering the local anaesthetic to the site of action any adverse effects associated with systemic toxicity may be minimised. However, the effective delivery of drugs into and through the skin is complicated and involves

extensive studies on the permeation characteristics of drug delivery systems.⁶

The human skin comprises of three tissue layers: the uppermost being the stratified, avascular, cellular epidermis which is the outermost and non- viable layer of the skin, it acts as a protective barrier for the body and is highly difficult to transverse.⁷ The Stratum corneum mainly consists of intercellular lipids which are made up of ceramides, cholesterol, cholesterol esters, and free fatty acids. The organisation and unique chemical composition of these lipids render a high degree of water impermeability to the skin. The barrier function of the stratum corneum is provided by patterned lipid lamellae localized to the extracellular spaces between corneocytes which makes it difficult for transversing the membrane for both water and other permeates. The next layer which is the dermis consists of connective tissue, nerves and blood vessels and the lowermost layer is the subcutaneous fat layer which lies beneath the dermis.⁸

For therapeutic quantities of drug to permeate through the skin, the barrier properties of the Stratum corneum must be overcome. Because of the selective nature of the skin barrier, a select section of drugs can be delivered to the skin for local action at therapeutic levels. A lipophilic drug, can cross the Stratum corneum, but once it enters the more aqueous lower regions of the epidermis the rate of diffusion decreases. Thus, as the diffusion of a very hydrophobic permeate proceeds into deeper layers of the skin, diffusion slows, and the concentration gradient (from Stratum corneum down to the viable tissue) falls.⁹



Formulation of poorly water soluble molecules is a challenging task as they often exhibit low solubility in most topical vehicles. Topical formulations, such as ointments, which can solubilise high concentrations of hydrophobic actives, are oily and gritty thus making the formulation less acceptable for patients. A sufficient concentration of a topically applied therapeutic agent must be loaded into the vehicle to ensure an adequate concentration gradient between the formulation and the skin, in order to attain adequate release of the drug into the skin.¹⁰ Topical patches do not possess the capability to release the entire amount of the drug incorporated into the skin, and huge quantities of drug are wasted once the patch is peeled off from the skin.

Hence what is desired is a combination of aesthetically and cosmetically appealing gel and patch or a film capable of delivering required quantity of drug into the skin without having the disadvantages of a conventional patch.

Hence a formulation was attempted which would have the capability of forming a film on topical administration, on the skin. The film-forming polymer may be such as to form a transparent film after the evaporation of a portion of the solvent. The formulation on contact with the skin will form a semi occlusive film over the skin, thereby concentrating the active ingredient of the formulation in a matrix of the polymer.¹¹

The film-forming polymers used for topical administration, are polyvinyl pyrrolidone (PVP), polyvinyl alcohol (PVA), HydroxyPropyl cellulose (HPC), HydroxyPropyl Methyl cellulose (HPMC), various grades of Methacrylates and Ethyl Cellulose to name a few.

A local anaesthetic capable of blocking the nerve conduction potential of neuropathic sites is utilized in the present formulation to give symptomatic relief to patients experiencing neuropathic pain.

MATERIALS AND METHODS

Materials

Various grades of Hydroxy Propyl Methyl Cellulose (HPMC) were procured from local vendors, Hydroxy Propyl Cellulose (HPC) was a gift sample from DKSH, India, Methyl ester of glucose was a gift samples from Lubrizol, India and Chemspark Mumbai. Propylene glycol, PEG 400, glycerol were purchased from Qualigens. Ethanol from SD fine chemicals. All other reagents and solvents were AR grade and HPLC grade.

Formulation of gels

After preliminary trials with conventional polymers like PVPK 30, PVPK 90, HPC etc, the solubility of Ropivacaine was evaluated in novel polymeric systems which contained a blend of polysaccharide, a low molecular weight synergistic saccharide and a solvent was selected for topical delivery of drugs as it gave a quick drying, shiny, transparent film on drying.

Ethanol is particularly preferred as the vehicle, since it is capable of dissolving high quantities of most drugs suitable for topical administration and it dries quickly allowing the formation of a film adhering to the skin.

Accurate quantity of ethanol was weighed, covered with aluminum foil to prevent evaporation. 1.25% of Ropivacaine was weighed and incorporated. Weighed quantity of the polymer was added to it under constant stirring. Care was taken to avoid formation of air bubbles. A humectant was incorporated in to the drug-Ethanol-polymer gel mix and stirred to get uniform pourable transparent gel. Variations in the grades of polymer depending on the viscosity as well as in the humectants was carried out in order to achieve the optimized formulation as given in Table 1.

Table 1: Formulation of gels

Ingredients	F1	F2	F3	F4	F5	F6	F7	F8
	% w/w							
Drug	1.25							
Polymer of High Viscosity	15.00	20.00	10.00	--	--	15.00	15.00	15.00
Polymer of Low viscosity	--	--	--	15.00	20.00	--	--	--
Methyl Gluceth 20	5.00	5.00	5.00	5.00	5.00	--	--	10.00
Methyl Gluceth 10	--	--	--	--	--	5.00	10.00	--
Ethanol	Qs to 100							

Evaluation of gels

Formulations were subjected to evaluation of physical parameters like appearance, consistency, film characteristics and absence of skin irritation.

The criteria for selecting optimized formulations were, Quick drying time (less 1 minute), Shiny, transparent,

flexible and non tacky film, Gel like consistency with cohesive property to adhere to the skin.

Appearance of the gel and films

The appearance of the gels and the films formed after application of the gels was examined. The transparency, clarity and flexibility of the films were observed. Formulations which formed a transparent, shiny, adhesive



and flexible film on the skin were selected. Furthermore the appearance of the films formed after application of gels was visually observed under the microscope for uniformity of the film. A small amount of methylene blue was dissolved in the gel and it was applied over a clean glass slide, allowed to air dry and observed at magnifications 10x and 40x on optical microscope.

Gels were evaluated for their physicochemical properties:

Viscosity

The viscosity of the prepared gels was measured using a cone and plate viscometer, at a controlled temperature of $30 \pm 2^\circ\text{C}$ m about 0.5 grams of the formulation was transferred to the plate and left to equilibrate. The viscosities of the formulations were determined in triplicate.¹²

pH

pH measurements were carried out on the gels using a digital type pH meter (Pico), by inserting the glass electrode completely into the gel system and waiting for stabilization of the pH.

Spreadability

Gel, 0.5 g was accurately weighed on a smooth flat surfaced glass plate. The initial diameter of gel was noted. Another glass plate of same dimensions was placed on the first plate over the formulation. A Standard weight was placed on the upper plate over the gel region for a period of 60 seconds. The weight and upper plate was gradually removed and final diameter of gel was measured. Spreadability was calculated using the formula:

$$\% \text{ Spreadability} = \frac{\text{Final diameter} - \text{Initial Diameter}}{\text{Initial Diameter}} * 100$$

Drug Content

Gel 100mg was dissolved a specified quantity of methanol, sonicated and diluted suitably using the mobile phase. The drug content was determined by a validated HPLC method.

Interaction studies of the drug and polymer

Presence of any undesirable interaction between the drug and the polymers was assessed using DSC studies. An accurate amount of Ropivacaine, polymer and Ropivacaine and polymer physical mixture kept under stress conditions of 40°C and 75% RH for 2 months, was weighed and transferred to the aluminium pans and the rate of heating was 10°C per minute from 35°C to 300°C . Any changes in the DSC thermograms were recorded.

The *ex-in vivo* drying time

The *ex-in vivo* drying time of the films formed after application of the gels was evaluated. A small quantity of the placebo gel was applied to the forearm of 5 volunteers whose written consent was taken after complete intimation of the procedure. The time required

for the gel to completely dry and form a film on the hands of the volunteers was recorded. Complete drying was checked by lightly pressing cotton over the films and visually examining remnants of fibres.

Quantity of drug which can be incorporated into the gel

The amount of drug which can be incorporated into the gel base without any adverse effects was evaluated. Parameters like transparency of the gel, stability of the gel on standing, precipitation of the gel, formation of transparent and shiny film over the skin and the washability and tackiness of the gels were evaluated over a small area on the fore arms of 3 volunteers. The volunteers had given prior written consent and were informed of the action of the drug with the assurance that the formulation would be washed off the skin in less than 2 minutes before absorption of drug takes place.

Texture Analyzer settings

The optimized gels prepared with a polymer concentration of 15% exhibited low viscosity and were unable to give sufficient resistance to the probe to record a reading. Hence to extrapolate the gel attributes, gels containing higher polymer concentrations were prepared and evaluated for their textural properties Stable Microsystems TA XT Plus instrument was used for the textural evaluation.

Various aluminium cylinder probes of different diameter were tried: 0.6mm, 6mm, and 1/2inch. Sufficient resistance to the gel formulations was obtained using 1/2 inch probe. The settings were optimized after trials and the pre-test, test and post-test speed of the penetration of the probe into the sample was set at 1.0 mm/s while the trigger force was 10g. The force and the time were plotted and the force of adhesion and cohesion was obtained.^{13,14}

Ethanol content remaining after application

An indirect method was developed to determine the amount of ethanol remaining after application of the gel to the skin. Gas chromatography was utilized for the determination of residence time of ethanol. Three sets of petri plates (Set I, II and III) were heated to 37°C in order to mimic body temperature. Each set contained three petri plates in order to obtain readings in triplicate. Equal quantity of weighed formulation was applied as a thin layer to the plates. A specific quantity of water was added to the set 1 after 1 minute, set II after 3 minutes and set III after 5 minutes to dissolve the un-evaporated organic solvents since water is miscible with Ethanol. After shaking and mixing well an aliquote was removed, it was then suitably diluted and injected into GC to determine the concentration of ethanol remaining.^{15,16}

In-vitro Diffusion Study

Drug Diffusion studies form the film forming gels was investigated through dialysis membrane-150, using modified Franz diffusion cells. The recipient compartment



contained 6.8 Phosphate buffer. In-vitro diffusion study of different formulations was carried out and the cumulative % drug diffused after 30mins, 1hr and thereafter every hour till 8hours were calculated.

Ex- vivo diffusion study

Ex vivo diffusion was carried out using the porcine ear skin as it mimics the human skin very well. The porcine ear was procured from the local slaughter house and cleaned with saline before separating the skin layer from the underlying cartilages. The fat layer along with the cartilages were dissected and separated from the skin and it was stored for 24 hours at -20°C. The skin was then thawed gently and carefully in order to preserve its integrity and spread over the receptor compartment so that the dermis is in continuous contact with the buffer. The gel was spread over the stratum corneum and drug diffusion was observed for 8 hours. An aliquote was removed at specific time intervals and diluted with the mobile phase before injecting into the HPLC, to determine drug content.¹⁷

Pharmacodynamic Evaluations

Anti-nociceptive studies were carried out using hot plate and tail flick tests on Wistar rats to test the efficacy of the formulation. The protocol was approved by the institutional animal ethics committee. The rats were divided into 3 groups containing 6 rats each for statistical evaluations. The animals were housed under standard conditions and had free access to feed and water. Hot plate and tail flick tests were employed as means of determining the level of anti-nociception induced due to the gels.¹⁸

Hot Plate Test

Ropivacaine film forming gel formulation in a concentration equivalent to conventional Lidocaine gels were applied to the paws of animals. The formulations were left to air dry for 1 minute before placing the animals back into their cages. The time points for recording the response of the animals to the stimuli were 1 hr, 2hrs, 4 hrs, 5 hrs and 7 hrs. The hot plate was heated to 55°C and the temperature of the plate was monitored and kept constant throughout the experiment. At each time point the animals were placed on it. Licking or scratching of the fore and hind paws or jumping was recorded as the response. A maximum latency period of 15 seconds was pre-decided in order to avoid any permanent damage to the tissue of the animals.

Tail flick test

Tail flick test was performed by tail immersion method where the tail of the rats was immersed in a hot water kept at a constant temperature of 55°C and monitored by the use of a thermometer suspended into it. Ropivacaine Gels and the conventional Lidocaine gel were applied from the tip of the tail of animals to about a distance of 5 cm above it and were left to air dry for 1-2 minutes. The time points for the study were selected as 2 hours, 4

hours and 6 hours. The time points selected were limited due to the possibility of the film gels being washed off from the tail after immersion in water. The latency of tail withdrawal from the heat source which was the hot water bath in this experiment was recorded.

Skin irritation and Histopathology

The Draize patch test and histopathological study evaluations were carried out using Wistar rats. The hair around the dorsal region of the rat skin was removed using clippers and a hair removing cream, it was observed for 24 hours in order to assess any local irritation or damage due to the hair removal process. The gel was applied for 24 hrs keeping the area bandaged in order to avoid any scratching and removal of film forming gel formulation by the rats. After 24 h, the rats were observed for redness, swelling, erythema, and were scored as follows. No Erythema = 0, very mild erythema = 1, Moderate Erythema = 2, Moderate to severe erythema = 3, Severe Erythema (Extreme redness and soreness) = 4. The rats were sacrificed after a period of 14 days using cervical dislocation. The rat skin was removed from the dorsal area, further dissected and fixed in a 10% formalin solution. Further processing was carried out by staining with eosin and hematoxylin for viewing under the microscope.

Stability Studies

The gels were charged for stability at 25°C/60% RH as well as accelerated stability at 40°C/75% RH according to the ICH guidelines. Additional samples were stored under refrigeration at 4°C. After 1 month, 2 months and 3 months of accelerated conditions samples were withdrawn and were assessed for appearance, clarity, film formation time, drug content and *in-vitro* diffusion.

RESULTS AND DISCUSSION

Various trials were conducted and the appearance of each formulation was assessed. It was observed that the all formulation development trials resulted in gels that were transparent, clear elegant and aesthetic in appearance. There was no entrapment of air and the nature of the gels was flowable. When observed under the microscope a uniform film was seen without any breaks or any wrinkles as depicted in figure 1.



Figure 1: Appearance of film formed after application of gel a) under 40x magnification b) under 10x magnification

Viscosity

The apparent viscosity of the gels ranged between 800 – 1900cps. Gels containing 10 percent of polymer were highly free flowing while those with 20% and 25% polymer content were had a viscosity of ~1600-1900 respectively. The optimum concentration of the polymer was found to be 15% and showed a viscosity of 1300cps. They were not highly viscous and easily flowable gels. This property is important because highly viscous and firm gels require rubbing onto the skin which generates friction. This friction may cause allodynia in patients suffering from neuropathic pain.

pH

The pH of the gels was found to be around 6.5 – 7.2. This can be considered to be the appropriate pH for topical application to the skin.

Spreadability

The spreadability of all gels was found to be over 80 % as calculated from the formula given previously. This can be attributed to the lower viscosity and flowability of the gels.

Drug Content

The drug content in the gels ranged from 97% to 102%.

Interaction studies

The DSC studies of the drug and the drug polymer mixture after accelerated stability studies for 2 months were carried out and the results are shown in figure 2, Ropivacaine drug exhibited an endothermic peak at 147°C, which is also observed in the drug polymer physical mixture; this indicated that there was no interaction and incompatibility between the drug and the polymer.

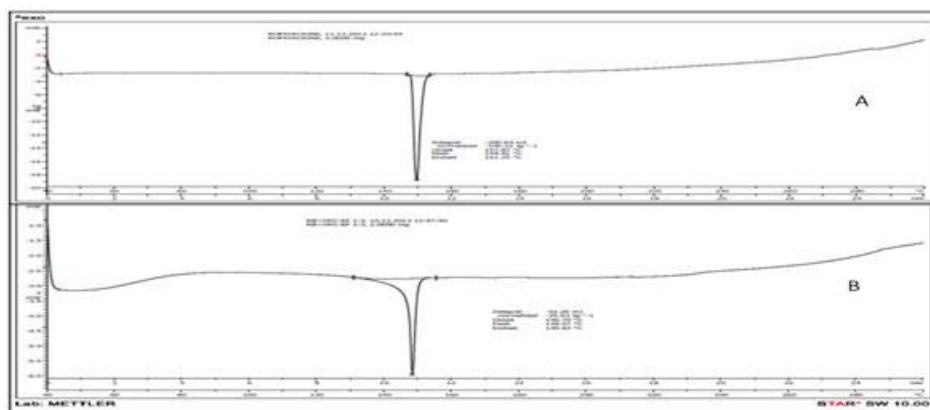


Figure 2: Interaction between the drug and polymer observed using DSC endotherms, A: Drug alone, B: Mixture of drug and polymer

Ex in vivo drying time

For a gel to be patient compliant it should not cause inadvertent staining of the clothes or other materials it comes in contact with. It should not get rubbed off on surfaces, at the same time it should be quick drying and easy to apply. Hence evaluation of the drying time poses to be a critical parameter in the formulation of film forming gels. It is a challenge to formulate a gel with the optimum balance between the spreadability, drying time and viscosity. A gel which spreads easily and has low viscosity accompanied by a low drying time may be too The drying time of the gels when spread as a thin layer over the skin to form a film was found to be in the range of 20 seconds to 50 seconds. Gels which had a higher polymer concentration of 20% - 25 % showed a high drying time of around 40 – 50 seconds while those with lower concentration of 10% - 15% had a drying time of 20 – 40 seconds.

Amount of drug incorporated

In order to evaluate the suitability of the film forming gel system for incorporation of higher quantity of drugs, 5, 10, 15 and 20% of Ropivacaine was loaded in the gels. Gels with the above mentioned concentrations of

Ropivacaine appeared transparent and clear. However when with informed consent, ex-in-vivo evaluations of these gels were carried out till a concentration of 10% of Ropivacaine the film formed was transparent, clear and shiny, but as the concentration of Ropivacaine was increased to 15% the films formed were transparent but they lost their shine and had a matt finish. At 20% concentrations the film appeared as a translucent to whitish patch over the skin which was not a desirable quality. Therefore it was concluded that the film forming gel can incorporate a maximum of 10 % drug without any adverse effects on the aesthetic appeal and appearance of the film formed after application of the gel.

Analysis of texture of the gel

The peak or maximum force needed for penetration into the gel was taken as a measurement for firmness/hardness as observed in figure 3. The higher the value of the force the firmer and more difficult for external penetration is the sample. The consistency of the gel is measured by calculating the area under the upward curve i.e the 1st curve obtained when the probe penetrates into the sample. A higher value indicates that the sample is thick and viscous in consistency. The

negative curve of the graph, which is obtained as the probe is pulled out of the gel and returns to its original position, is the adhesiveness/ cohesiveness of sample which retards the upward motion of the probe while being pulled out of the gel. The area of the negative region of the curve is called as the work of cohesion, the higher the value the more resistant to withdrawal of the probe is which indicates that the sample is highly cohesive or sticky. this factor is important in film forming gels as its necessary for the gels to stick or adhere to the surface of the tissue in order to form a film over it.

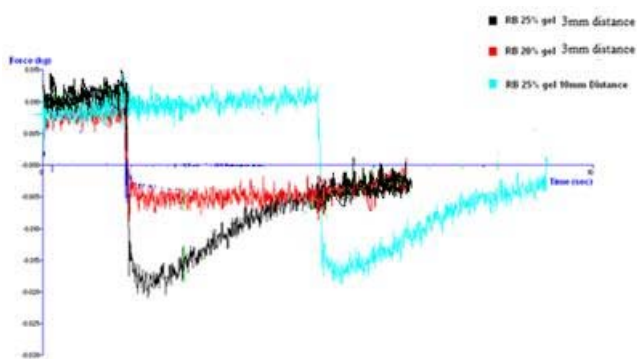


Figure 3: Texture analysis of gels showing the firmness as well as adhesiveness and cohesiveness of gel

Evaporation of ethanol

The content of ethanol at the end of 1 minute and 3 minutes was found to be negligible. At the end of 5 minutes it was not detected indicating that the entire ethanol had evaporated.

In-vitro drug Diffusion

Drug diffusion through the dialysis membrane was found to be very high indicating good permeation characteristics of the gel. The gel with a high polymer concentration showed slight retardation in the diffusion as compared to the gels with low or medium concentration of polymers. Above 85% drug diffusion was obtained with gels containing 15% of polymer concentration as seen in figure 4, while those with low polymer concentration showed over 90% drug diffusion. This indicated that viscosity of the film forming gel is an important consideration while formulating film forming gels of Ropivacaine

Ex-vivo drug diffusion

The optimized formulation was further evaluated for ex-vivo diffusion using the porcine ear skin. The skin being a significant barrier retarded the diffusion of Ropivacaine significantly as seen in figure 4. The flux of the film forming gel was found to be 211µg/hr/cm². This can be considered as a high flux value indicating good permeation characteristics of the gel.

Anti-nociceptive activity

The optimized film forming gel was evaluated against the negative control i.e placebo as well as the commercially available Lidocaine gel. This study proves valuable in assessing the capacity of the film forming gel to inhibit

symptoms of pain compared to the marketed formulation. Lidocaine was selected as the standard, since it falls into the same class of compound as Ropivacaine and it has the same pathway of pain blockade as that of Ropivacaine i.e. by causing depolarisation of the sodium channels.

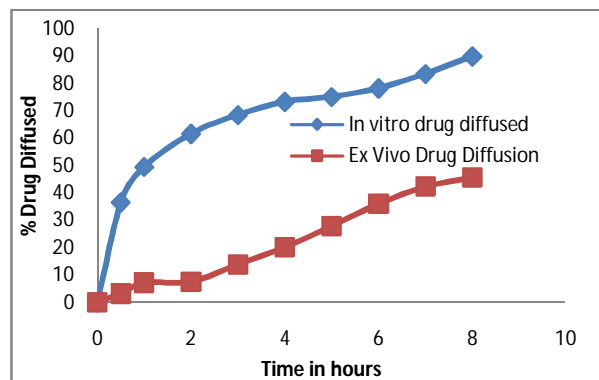


Figure 4: In-vitro and Ex vivo Diffusion of the optimized formulation

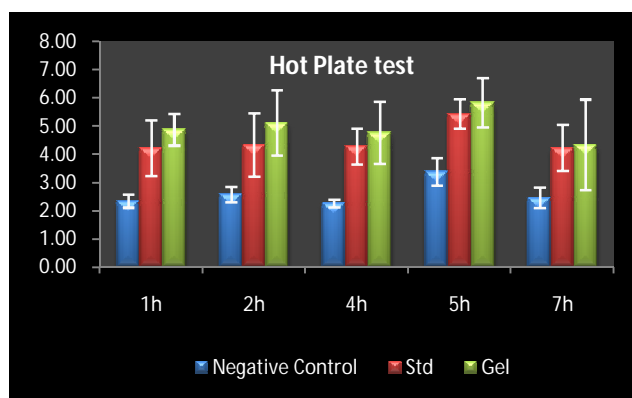


Figure 5: Anti-nociceptive activity by hot plate test in rats shown by negative control, standard and film forming gel

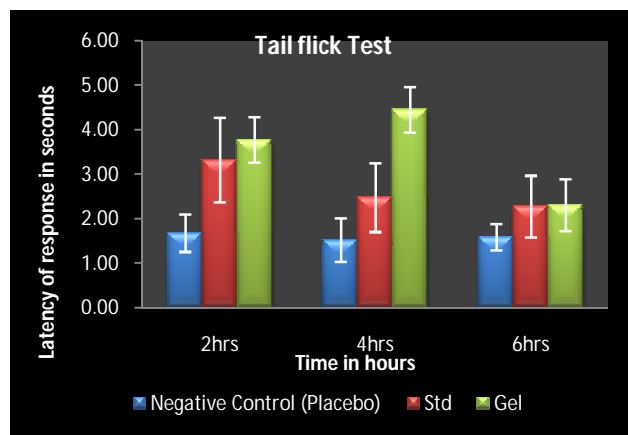


Figure 6: Anti-nociceptive activity by tail flick test in rats shown by negative control, standard and film forming gel

The anti-nociceptive activity studies, using both hot plate test and tail flick tests indicated that the optimized film forming gel was more efficacious in inhibition of pain, as the latency time before the response given by the rat in case hotplate as well as tail flick test is much higher than the standard Lidocaine gel. The P ≤ 0.05 were considered

as statistically significant. Compared to the negative control the film forming gel showed a much higher latency period. Comparisons between the film forming gel and the marketed Lidocaine gel indicated that there is insignificant difference between the pain inhibition except at the fourth hour where the pain inhibition capacity is higher than that of the conventional gel as observed in figure 5 and 6. This implies that the capacity of the film forming gel to inhibit pain is equal to or better than the conventional Lidocaine gels. The inhibition of pain perception was sustained over 7 hours, which corroborates with the results observed in the *ex-vivo* drug diffusion studies where the drug was diffused over a period of 8 hours and showed sustained delivery.

Histopathological studies

The histopathological studies revealed that the film forming gel did not produce any irritation to the skin. There was no erythema and the score in all rats was 0 to 1. There were no lesions observed neither was there any significant change in the skin or any break in length of epithelium. No ulceration was seen as observed in figure 7. Hence Ropivacaine film forming gels may be considered as a safe option for application onto the skin.

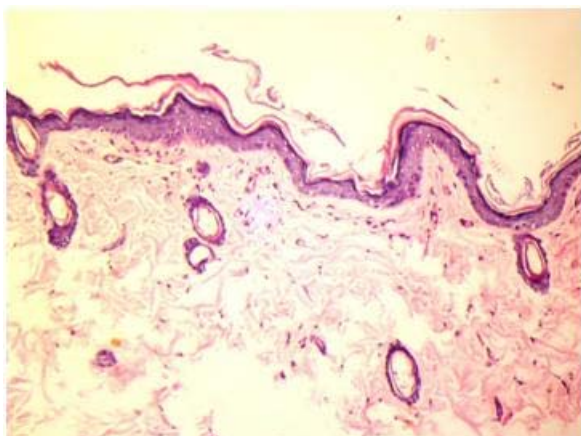


Figure 7: Histopathological evaluations of skin section after application of film forming gels

Stability studies

The film forming gels were kept on stability in the final container and closure i.e Lami Tubes at room temperature, at 40°C and 75% RH for accelerated stability and at 4°C in the fridge. Stability Studies after 1, 2, 3 months indicated that no change in colour, odour, appearance or assay was observed. *In-vitro* Diffusion studies were performed and there was no change observed in the diffusion profile after 3 months of accelerated stability.

CONCLUSION

The film forming gels present a novel platform to deliver large quantities of drugs to the skin. Film forming gel of a local anaesthetic, Ropivacaine, was formulated with an elegant appearance and aesthetic appeal. These

formulations have the potential to inhibit pain and may be topically applied for neuropathic pain management.

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