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CHALLENGES IN TRANSDERMAL FORMULATION: IN VITRO EVALUATION

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ABSTRACT

One of the most vital challenges for Transdermal Therapy is the skin, itself acting as a barrier. Hence, in this study, an attempt was made to elucidate the transdermal permeation potential of Surfactant (Brij-58 & Brij-30)in comparison to terpene (clove oil) using Aceclofenac as a model drug. The *in vitro* skin permeation studies for aceclofenac in various drug solutions revealed that the drug in Isotonic phosphate buffer was able to permeate skin with a flux which is not significant for transdermal permeation from any formulation. Addition of co- solvent (ethanol 95%) resulted in an increase in the flux. Different skin permeation enhancers were tried in an attempt to increase permeation of the drug in order to achieve the desired plasma concentration of aceclofenac. Enhancers tried included, Brij-58, Brij-30 and Clove oil. All skin permeation enhancers increased the flux of drug with respect to their respective controls. An increase in both the flux as well as permeability coefficient of the drug was seen when the concentration of enhancers was increased from 1% to 2% in case of Brij-58 and Brij-30 and from 1-10% in case of Clove oil. On the basis of these studies 2% Brij-58 which showed highest permeation potential was selected as permeation enhancer for the design of Transdermal Therapeutic System.

Keywords: Transdermal Therapeutic System, Permeation enhancement, Surfactants.

INTRODUCTION

NSAIDs are amongst the most widely used of all therapeutic agents. They are frequently prescribed for the long-term treatment of rheumatic musculoskeletal complaints. These are the drugs of first choice for the management of variety of chronic inflammation and chronic degenerative orthopathies.The major drawback of anti-inflammatory drug use is the preponderance of gastrointestinal side effects encountered with majority of agents. As these drugs are generally given for a longer duration of time, they cause gastrointestinal disturbances which are generally recognized to be due to interference by the drug with the biosynthesis of prostaglandins and other arachidonic acid metabolites in the gastric mucosa. These drugs also undergo substantial hepatic first pass metabolism and only small fraction of the drug reaches systemic circulation. This originates the need of an alternative route of administration, which can by-pass the gastro-hepatic metabolism of the drug. Transdermal route is an alternative choice of route of administration for such drugs. This route is a self-contained discrete system which when applied to the intact skin, delivers the drug through the skin at a controlled rate to the systemic circulation. Over the last 15 years, a tremendous amount of work has been directed toward the search for specific chemicals, or combinations of chemicals, that can act as penetration enhancers. In this quest for the identification of ideal penetration enhancer, Brij-58, a nonionic Surfactant seems to help in achieving the goal which when added to formulations solubilize lipids within the stratum corneum and thus have the potential to enhance permeation.

Thus, it is anticipated that transdermal delivery of Aceclofenac will result in the release of drug at

appropriate rate to maintain suitable plasma drug levels for the therapeutic efficacy by using skin as the port of the entry of drugs using Brij-58 as penetration enhancer.

MATERIALS AND METHODS

In order to establish the effect of various penetration enhancers on the permeability of the drug, the skin permeation studies were carried out. [1] The preclinical study protocol for entire study was approved by Institutional Animal Ethics Committee (Reg. No. 801/03/CA/CPCSEA) No. F-IAEC (Pharm.Sc.) approval /04/06-08.

1. Fabrication of diffusion cell for preliminary skin permeation studies: A horizontal glass diffusion cell was used for preliminary studies. The cell was fabricated by a local fabricator and consisted of two half cells, the donor and the receiver, which were held together with springs. The area of diffusion between two half - cells was 2.37cm^2. The capacity of each cell was 10 ml.

2. Selection of animal model: A fairly good number of species have been reported as animal models for skin permeation studies either in vitro or in vivo e.g., rabbit. Albino rat was selected for this work because of its easy availability. [2-8]

3. Procedure for skin permeation studies:

a. Skin treatment: Albino rats were sacrificed with prolonged ether anesthesia. The skin was excised from the abdominal region and was stored in the freezer until use. On the day of the experiment the skin was brought to room temperature and then hair and fat were removed manually. Skin was cut and trimmed to appropriate size and mounted between the two half cells of the fabricated apparatus. The stratum corneum of the skin faced the drug donor compartment whereas dermis faced the receiver compartment and the apparatus was assembled using springs. The donor compartment was empty while the receptor compartment was filled with Isotonic Phosphate Buffer (IPB pH 7.4). The receiver fluid was stirred with a magnetic rotor at a speed of 100 rpm and the assembled apparatus was placed in a hot air oven and the temperature was maintained at 37±0.5ºC.

b. Permeation Studies: After the pretreatment and stabilization of skin, the receptor compartment was filled with fresh IPB (pH 7.4). The donor compartment was filled with the drug solution (2 mg/10ml) prepared in various vehicles used for the study, with or without penetration enhancers. The samples were withdrawn (1ml) at different time intervals up to 24h and analyzed by UV spectrophotometric method at 276nm. The graphs were plotted between the cumulative amount of drug permeated (µg/cm^2)Vstime (Figure).The flux (Permeation rate) of the drug was determined directly from the slope of the regressed curve plotted as the amount of drug permeated (µg/cm^2) Vs time. The permeability coefficient (cm/hr) was calculated as the quotient of flux and drug concentration in the donor compartment.

RESULTS AND DISCUSSION

The *in vitro* skin permeation studies for aceclofenac in various drug solutions revealed that the drug in isotonic phosphate buffer was able to permeate skin with a flux of 7.01µg/cm^2/h, which is significant for transdermal permeation from any formulation. Addition of co solvent (ethanol 95%) resulted in an increase in the flux. This was because ethanol itself alters the permeability of the skin. Different skin permeation enhancers were tried in an attempt to increase permeation of the drug. Enhancers tried included, Brij-58, Brij-30 and Clove oil. All skin permeation enhancers increased the flux of drug with respect to their respective controls. Co-solvent (ethanol 95%) was used along with IPB (pH 7.4) (1:4) for permeation enhancers which were not soluble in IPB (pH 7.4).

Therefore for Brij-58 & Brij-30 the control was distilled water and for Clove oil, Ethanolic IPB (pH 7.4) was the control. The effect of different concentrations of Brij- 58, Brij-30 and clove oil on the flux of aceclofenac through the skin was determined. An increase in both the flux as well as permeability coefficient of the drug was seen when the concentration of enhancers was increased from 1% to 2% in case of Brij-58 and Brij-30 and from 1-10% in case of Clove oil. On the basis of these studies 2% Brij-58 was selected as permeation enhancer for the formulation of the transdermal System (Tables1-2 & Figure).

The highest flux achieved by nonionic surfactant, Brij-58 may be due to its large hydrophobic content (C_{16} in case of Brij-58) and to much greater oxyethylene content (OE) in Brij-58 (20 OE units) in comparison to Brij-30 (4 OE Units) indicating that the solubilization site of drug between the hydrophilic head groups of polyoxyethylene (POE) groups leading to the enhanced flux and permeability coefficient. Apart from this, increase in the flux can also be ascertained due to the hydrogen bonding

between the –OH and –NH group of surfactant and the Aceclofenac molecules respectively.

CONCLUSION

From the above study, it can be anticipated that Transdermal delivery of aceclofenac is feasible using Brij-58 as penetration enhancer. However, it is also anticipated that the study needs in- vivo evaluation

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Table1: Permeation study of aceclofenac in various vehicles with or without penetration enhancers

Code	Vehicle in donor compartment	Vehicle in receptor compartment	Penetration enhancers (% w/w)
$AcGP_1$	Distilled water	IPB of pH 7.4	None
$AcGP_2$	IPB of pH 7.4	IPB of pH 7.4	None
$AcGP_3$	Ethanolic IPB of pH 7.4	IPB of pH 7.4	None
$AcGP_4$	Distilled water	IPB of pH 7.4	Brij 58 (1%)
$AcGP_5$	Distilled water	IPB of pH 7.4	Brij 58 (2%)
$AcGP_6$	Distilled water	IPB of pH 7.4	Brij-30 (1%)
$AcGP_7$	Distilled water	IPB of pH 7.4	Brij-30 (2%)
$AcGP_8$	Ethanolic IPB of pH 7.4	IPB of pH 7.4	Clove oil (1%)
$AcGP_9$	Ethanolic IPB of pH 7.4	IPB of pH 7.4	Clove oil (5%)
$AcGP_{10}$	Ethanolic IPB of pH 7.4	IPB of pH 7.4	Clove oil (10%)

Drug concentration in donor compartment was 0.2 mg/ml (200µg/ml)

Table 2: Effect of various permeation enhancers on the permeability of aceclofenac

Solution code	Drug Solution	Permeability coefficient (Pb) x 10^{-2}(cm/h)
P_1	Distilled water (control -1)	2.865
P_2	IPB	3.01
P_3	Ethanolic IPB (control-2)	3.2
P_4	Brij-58 (1%)	5.66
P_5	Brij-58 (2%)	6.83
P_6	Brij-30 (1%)	3.82
P_7	Brij-30 (2%)	4.46
P_8	Clove oil (1%)	3.39
P_9	Clove oil (5%)	3.58
P_{10}	Clove oil (10%)	3.63

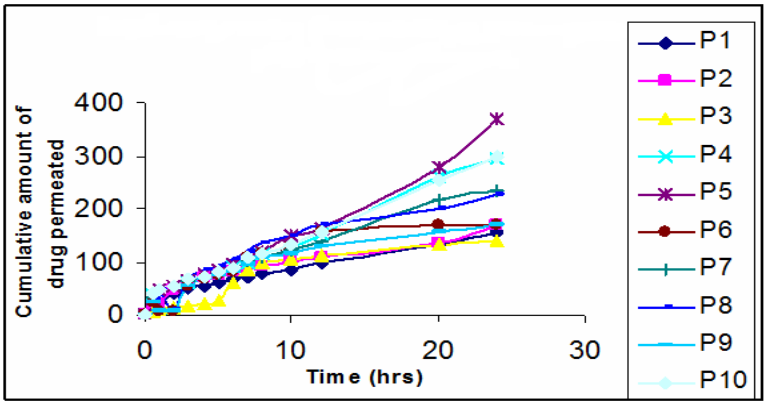

Figure: P5=Brij-58 (2%); P7=Brij-30(2%); P10=Clove Oil (10%) P1, P2, P3, P4, P6, P8, P9) =Different concentrations of enhancers used

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