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IN VITRO PENETRATION STUDY OF DICLOFENAC SODIUM USING THE HUMAN CADAVER SKIN

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Keywords:

Diclofenac sodium, In vitro penetration, Franz diffusion cell, Human cadaver skin

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ABSTRACT

The skin is very effective as a selective penetration barrier. Percutaneous absorption involves the passage of the drug molecule from the skin surface into the stratum corneum under the influence of a concentration gradient and its subsequent diffusion through the stratum corneum and underlying epidermis, through the dermis, and into the blood circulation. There is currently a great deal of world-wide interest in the field of transdermal drug delivery and, consequently, broad classes of drugs are being evaluated for percutaneous absorption potential. The advantages of this mode of drug administration are numerous, the patient convenience and therapeutic optimization of using patch transdermal systems being major positive features. The in vitro release test is a measure of in process control and also as a finished product specification for example, gels, emugel and spray. An in vitro diffusion cell experiment was designed to demonstrate the rate of release of Diclofenac sodium from three different topical formulations: (i) gels, (ii) emugel and (iii) spray. In vitro release of Diclofenac sodium from three different formulations through the receptor phase through human cadaver skin was monitored chromatographically. By monitoring and attempting to explain the numerous possible from the three formulations, it was a better to understanding of the complexities of transdermal drug administration. More over spray topical formulation could be suggested as a good dosage form for the topical delivery of Diclofenac sodium, giving higher drug release than the gel and emugel formulations.

Introduction:

The skin is the largest human organ. It ensures that harmful substances and drugs released from topically applied formulations cannot intrude into the organism offhand [1]. Drug delivery through the skin has been used to target the epidermis, dermis and deeper tissues and for systemic delivery. The major barrier for the transport of drugs through the skin is the stratum corneum, with most transport occurring through the intercellular region. When taken orally, many drugs are destroyed by the liver. Drug administration through the skin often provides a slower, more controlled alternative route for release into the blood stream. There is currently a great deal of world-wide interest in the field of trans-dermal drug delivery and, consequently, broad classes of drugs are being evaluated for percutaneous absorption potential. Another potential ad-vantage of this type of drug delivery is the optimization of drug concentration at the desirable sites, reducing the chances of side effects [2]. Therapeutic efficacy of any topical formulation depends on its ability to deliver drugs to their sites of action from the skin surface for either local or systemic purposes. [3, 4]. Diclofenac sodium (2-[2-[(2, 6-dichlorophenyl) amino] phenyl] acetic acid) is a potent member of non-steroidal anti-inflammatory drugs (NSAIDS) and widely used clinically, because of its strong analgesic and anti-pyretic effect [5].It has a short half-life (2 hrs). Diclofenac sodium causes gastrointestinal disturbances, peptic ulceration with bleeding, if present in large doses in gastrointestinal tract [6].It is marketed as injections, oral sustained release tablets and topical formulations. After oral administration, it is extensively metabolized in the liver and because of its short biological half-life, the drug has to be administered frequently [7]. The topical application allows for a higher local concentration of the drug at the site of initiation of the pain and lower or negligible systemic drug levels producing fewer or not adverse drug effects [8]. Topical drugs used to control pain act locally on damaged or dysfunctional soft tissues or peripheral nerves, and their actions may be on the inflammatory response itself or on sensory neurons [2]. A Diclofenac formulation with a high degree of skin permeation could be useful in the treatment of not only locally inflamed skin tissues, but also inflammatory and painful states of supporting structures of the body bones, ligaments, joints, tendons and muscles [9, 10]. The present work aims to evaluate that in vitro release of Diclofenac sodium from the different formulations.

Material and Method:

Materials:

Three marketed Diclofenac formulations [Test drug A- Diclofenac Gel B.P. 15 gm; Defenac Gel Lic. No.: K/01/07-08/131 Batch No.: ADN902, Mfg. Date: 02/2009, Exp. Date: 01/2012, Mfg. By: LUPIN LTD,Mumbai.; Test drug B Diclofenac Diethylamine BP 30 ml Spray; Duoflam Spray, Lic. No.: AD/248-A, Batch No.: 8001, Mfg. Date: 04/08, Exp. Date: 04/2011, Mfg. By: SVIZERA HEALTH CARE, Mumbai and Test drug C- Diclofenac Gel B.P. 30 gm; Voveran Emulgel, Lic. No.: KTK/25/460/2001, Batch No.: 8Z099T, Mfg. Date: 12/2008 Exp. Date: 11/2011, Mfg. By: Novartis India Ltd., Bangalore] were used for in vitro permeation study.

The Franz diffusion cell was used to determine the amount of the drug diffused from different formulations.

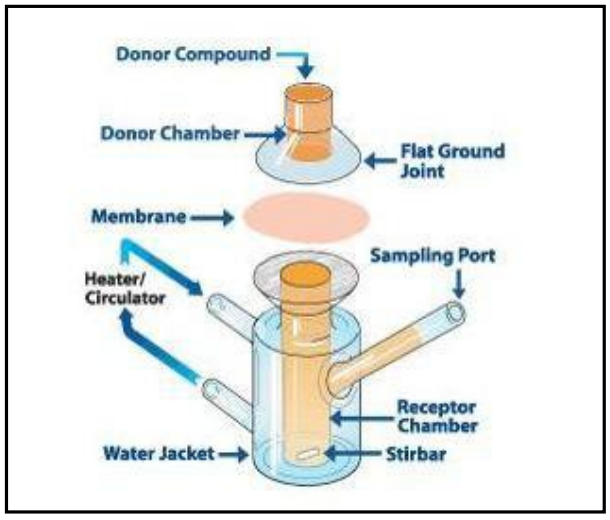

Figure 1: Franz diffusion cell

Method:

Vertical Franz-type diffusion cells with a diffusional surface area of 1.76 cm^2 were used to study the permeability of Diclofenac Sodium. The skin patches of 5 cm^2 were collected from Government Medical College, Aurangabad. The skin was applied with the drug on its epidermal surface. 1 g of gel and emugel formulation of Diclofenac sodium were packed into cell donor chamber, ensuring that there were no air bubbles between the formulation and donor surface of the human cadaver skin. Similarly for spray formulation to get the same amount of drug equivalent to gel and emugel formulation, it was sprayed for 10 seconds. The

holders containing the skin and formulation were then placed on diffusion cells using a spring clamp. The receptor phase was filled with phosphate buffer pH 6.8 and continuously stirred with a small magnetic bar at a speed of 100 rpm during the experiments to ensure homogeneity and maintained at 37±0.5^{0}C. The 2 ml samples were withdrawn at 0, 30, 60, 90 minutes respectively for each of the formulations of Diclofenac sodium. Simultaneously equivalent amount of phosphate buffer pH 6.8 was added to maintain the volume of receptor Phase.

The samples withdrawn from the port were taken in a 25 mL volumetric flask and acidified by adding 1 mL of 0.1 N HCl. To this solution, 10 ml of cyclohexane was added and the flask was stoppered and shaken vigorously for 10 minutes. The organic layer was separated and dried under vacuum. The dried residue was then dissolved in 5 ml of diluents (water and methanol (30:70) v/v), and the tubes were shaken vigorously for 15 minutes and sonicated. The solution was then filtered through 0.45 µ membrane filter and then analyzed using HPLC method at 276 nm.

Results:

Diclofenac sodium was incorporated with various topical formulations. Different release profiles of Diclofenac sodium were observed in all the formulations. The spray formulation appears to present the ideal combination of solubility and physical diffusivity through the vehicle, yielding the highest drug release rate.

The amount of drug permeated through the skin preparation was estimated by HPLC method and the results are represented in table below.

Time in Minutes	Amount in µg of Diclofenac Penetrated through the *In Vitro* Skin Preparation		
	Formulations A Gel	Formulations B Spray	Formulations C Emugel
30	43.9	41.8	39.8
60	56.07	61.8	51.8
90	72.84	78.3	71.2

Table 1: Amount of Diclofenac Penetrated through the *In Vitro* Skin Preparation

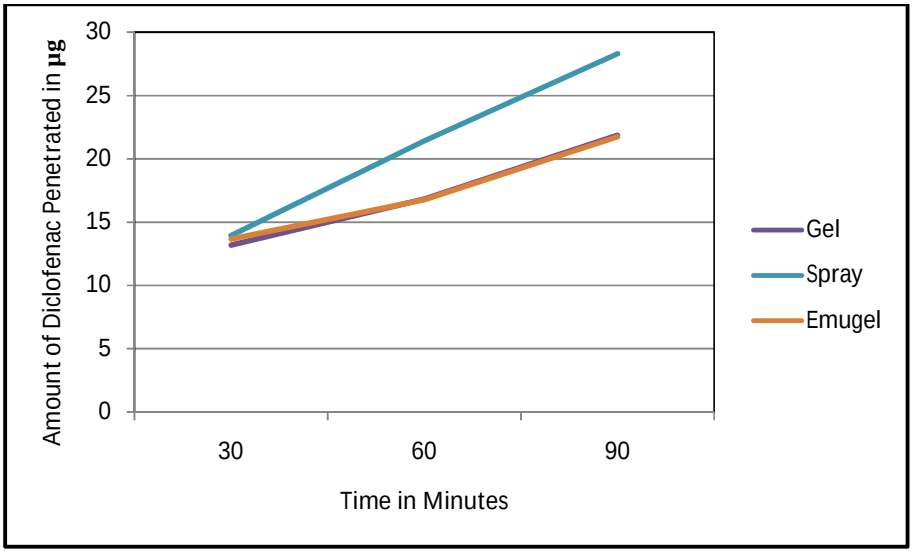

Figure 2: Comparative plot of Amount of Diclofenac penetrated from the Cadaver skin with respect to time for each formulation

Conclusion:

In *invitro* experiment for the penetration study of Diclofenac using the human cadaver skin, the graph plotted against the amount of Diclofenac penetrated with respect to time for each formulation reveals that, the Diclofenac penetrates steadily by following the zero order kinetics. The results showing the faster absorption trends by spray formulations and with little difference in the absorption characteristics of Gel and Emugel formulations. Thus it could be concluded that, the spray formulation attains the higher tissue concentration faster than the Gel and Emugel formulations and thereby can achieve its pain relieving effect faster. Also it could be stated that, the *invitro* penetration studies are reliable tools for the pharmacokinetic predictions of the topical formulations.

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