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Brief Note

Salicylic acid permeation: A comparative study with different vehicles and membranes

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ABSTRACT: Considering the skin´s function, different dermal pharmaceutical forms can be developed according to the type of therapeutic activity, active principle and excipients involved in the formulation, such as "transdermal preparations". In the present study, the permeation parameters of the non-steroidal anti-inflammatory drug, salicylic acid (SA) through synthetic membrane, polyvinyliden difluoride, and a biological membrane, egg shell membrane, with different vehicles, propylene glycol, isopropyl alcohol and carbopol gel, were determined. The reported physicochemical parameters of SA from CG were significantly higher than those obtained using PG and IP. This is attributed to the lipophilic nature of the vehicle that facilitates the release and penetration of the active principle, thus acting sinergically. The permeation profiles of SA allow us to state that permeation kinetics is of first order, so that the flux values obtained are in direct proportion to the specific rates of drug release.

Introduction

Percutaneous absorption involves the passage of a 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 (Sinha and Kaur, 2000). It provides two possible routes of cutaneous penetration: a transcellular route and an intercellular route, which is tortuous but continuous through the intercellular lipids (Hadgraft and Guy, 1989).

The transdermal mode of drug administration offers several distinct advantages since the application of a patch-like device to the skin surface is a non-invasive procedure that allows continuous intervention (Nauk *et al*., 2000). Generally, *in vitro* liberation studies are carried out in horizontal or vertical diffusion cells. Therefore, conditions *in vivo* are better simulated, leaving the skin surface exposed to the environment (Ganem, 2001).

During the past few years, skin has been shown to be a suitable delivery route for drugs formulated in transdermal therapeutic systems (TTS). In a TTS, the vehicle reservoir or the membrane could be made rate-determining to control transport of the drug across the skin (Gabboun *et al*., 2001).

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It is important to consider the reasons for using synthetic membranes as biological models. In order to understand the underlying mechanisms of membrane transfer, it is desirable to reduce the number of variables and to produce results that can be analyzed (Hadgraft and Guy, 1992).

The purpose of this research is to find a synthetic membrane that simulate the behavior of biological membranes to establish the physicochemical determinants that control delivery and modulation of salicylic acid with different membranes and vehicles. For the underlying mechanisms of membrane transfer, it is desirable to reduce the number of variables and to produce results that can be analyzed.

Materials and methods

Chemicals

The following chemical products were obtained from commercial suppliers and used as received: Salicylic acid (SA) (Sigma-Aldrich); propylene glycol (PG) (Merck); isopropyl alcohol (IP) (Merck); carbopol gel (CG) (Rowe *et al*., 2004); phosphate buffer saline (PBS) (pH = 7.4, prepared according to Martindale The Extra Pharmacopeia (Reynolds, 1989).

Membranes

17% PVDF (polyvinylidene difluoride) provided by Laboratorio de Ciencias de Superficie y Medios Porosos, U.N.S.L., and egg shell membrane.

Preparation of solutions

The saturated solution of SA in PG or IP were prepared according to literature data (Días *et al*., 2000). When CG was used as the vehicle, a gel base was prepared and the active principle was incorporated at 2% (w/w).

Experimental procedures

The Microette system (Hanson Research) used has diffusion vertical cells with a capacity of 4.5 ml equipped with a thermostatic bath, injection system, vacuum pump, agitation clamp, computerized sip control mod-

TABLE 1

Physical and physicochemical parameters and pre-treatment conditions of salycilic acid permeation *in vitro.*

Membrane	$\Delta X \times 10^4$ (cm)	Pre-treatment membrane-vehicle	$J_m \times 10^7$ (g/cm^2.s)	$P \times 10^6$ (cm/s)	$D \times 10^8$ (cm^2/s)
PVDF	280.0	PG-PG	6.068	3.144	8.803
		IP- IP	4.573	2.078	5.819
		--- - CG	7.038	35.19	98.53
		PBS-CG	5.261	26.31	73.65
Egg shell	198.0	PG-PG	9.568	4.957	9.816
		IP- IP	4.147	1.884	3.732
		PBS-CG	3.796	18.98	37.58

ΔX: membrane thickness; J_m: flux; P and D: permeation and diffusion coefficients; PG: propylene glycol; IP: isopropyl alcohol; PBS: phosphate buffer saline; PVDF: polyvinylidene difluoride.

ule and sampler. The membranes were cut to appropriate sizes and previously equilibrated with PBS (or PG or IP) for 20 h, being the effective permeation surface 1.767cm^2. All the system was maintained at 32±1°C with a circulating water jacket. Drug concentration in the receptor compartment was determined by UV-Vis spectrophotometry (Spectrophotometer Shimadzu UV 160 A). The SA detection was operated at 207 nm and 32±1°C. Experiments were performed in quadruplicate.

Results

The flux (J_m) of a drug through the stratum corneum under stationary conditions, can be described by Fick´s First Law:

$$J_m = D.\ \Delta C/\ \Delta x\ = Q_m/(t.A) \qquad (1)$$

where J_m is the amoung of mass diffusing across of a plane of area unit per time unit, D is a constant of proporcionality known as the diffusion coefficient and ($\Delta C/\Delta x$) is the change in concentration across the membrane. This reordered expression permits to determine total mass transfered *per* time unit from the slope of the lineal zone of the graph "quantity of permeation *versus* time". The permeation coefficient P (cm/s) can be calculated as the quotient between the flux and the concentration of the substance in the donor compartment (g/cm^3). Furthermore, the expression (1) allows an estimation of the diffusion coefficient D (cm^2/s) (Hadgraft and Guy, 1992).

Quantities permeated of salicylic acid in carbopol gel *versus* time using treated PVDF and egg shell membranes are shown in Figure 1. Due to it is not easy to determine accurattely from the lag-time neither the values of permeation (P) nor diffusion (D) coefficients, all diffusion experiments were performed through different membranes pre-treated with the vehicle obtaining absence of t_{lag}. The parameters values estimated from the diffusion profiles obtained for SA with different membranes and vehicles are listed in Table 1.

On the other hand, the fraction of the active principle released is frequently expressed by the equation $Q_t/Q_o = k.\ t^{1/2}$, where the constant k expresses the rate of drug diffusion, also related to the interaction between the drug and the vehicle. Figure 2 shows the linearity obtained when the values of the fraction of the released active principle (Q_t/Q_o x 100) were plotted against the square root of time for the experiments carried out using CG with the pre-treated membranes.

Discussion

The synthetic PVDF membrane was chosen due to similar characteristics to those of the human skin, such as high hydrophobicity, high chemical and thermal resistance, resistance to UV radiations, malleability and excellent mechanical properties (Ochoa *et al*., 2003). This membrane is asymmetric and acts as a selective barrier with very small pores.

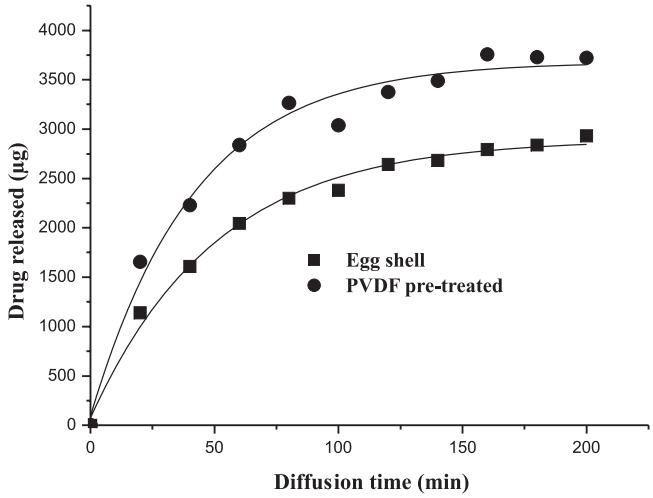

FIGURE 1. Salicylic acid permeation profiles in carbopol gel through PVDF and egg shell membranes pre-treated.

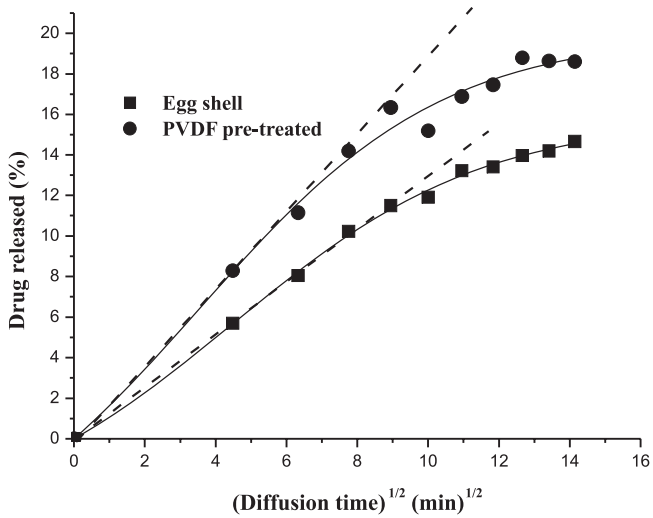

FIGURE 2. Linearized forms of released of SA in CG as a function of the square root of time for PVDF (k=1.820; r=0.999; SD=0.585) and egg shell membranes (k=1.298; r=0.999; SD=0.0687) pre-treated with PBS.

The parameters values estimated for the diffusion profiles obtained for SA in PG listed in Table 1 show that, using a simple biological membrane as the egg shell membrane, J_m value, P and D coefficients are higher than those found with the PVDF membrane which is a consequence of the biological membrane thickness.

The values of J_m, P and D obtained when isopropanol was used for the pre-treatment and as vehicle are similar for the membranes studied. It permits to conclude that this vehicle does not alter the membrane properties. On the other hand, these parameters are significantly different to those obtained when using PG, which is a consequence of the different interaction between the vehicle, the active principle and the membranes.

The physicochemical parameters P and D calculated for the SA permeation with carbopol gel as vehicle through PVDF (without treatment and pre-treated) and egg shell membrane are significantly higher than those obtained using PG and IP. This might be due to the vehicle lipophilic nature that facilitates the liberation and penetration of the active principle, thus acting synergically.

Different liberation profiles are obtained depending on the relative magnitude of the polymer swelling rate and the diffusion rate of the active principle (Vila Jato, 1997).

The profiles showed in Figure 2 correspond to kinetics of first order (n=1), with flux values (J_m) in direct proportion to the specific rates of drug liberation. At short times a linear ratio between the fraction of the released active principle and the square root of time is observed, liberation according to a Fickian mechanism.

The characterization of the membrane and the development of pharmaceutical strategies to increase availability of the appropriate drug will be helpful to find an optimal solution for some therapeutic problems related to percutaneous administration of drug. On the other hand, the use of *in vitro* methods permits to control laboratory conditions and to elucidate the individual factors that modify drug penetration.

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