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Some factors affecting the in vitro penetration of ibuprofen through human skin

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Summary

The influence of various factors on the permeation of ibuprofen across human skin in vitro was determined. Permeation was increased by increasing the volume fraction of water in binary water-transcutol solvent mixtures, probably due to changes in thermodynamic activity. Permeation was also increased in the presence of nonionic surfactants based on an oleyl alkyl chain although this effect was saturable. The data confirmed that it is possible to develop improved formulation strategies to optimise the delivery of ibuprofen across the skin.

Introduction

Ibuprofen is an effective drug in the treatment of rheumatoid arthritis and osteoarthritis. Recently there has been considerable interest in the potential usefulness of this drug when applied topically. A disadvantage of this route for drug delivery is that a relatively high dose is required to deliver therapeutic amounts across the skin and therefore evaluation of the potential for enhancement of the skin penetration of ibuprofen is of great practical importance. Previously (Bialik et al., 1991) we have reported the influence of certain vehicles on the transdermal flux of ibuprofen. In the majority of experiments full thickness human male skin was used and large differences in the rates of penetration between different skin samples were observed. This variability made it difficult to fully evaluate vehicle effects on percutaneous penetration. The purposes of the present study were to determine the influence of skin thickness on permeation and to investigate the effects of (a) alteration in permeant thermodynamic activity in the vehicle and (b) the presence of nonionic surfactants based on an oleyl alkyl chain.

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Materials and Methods

Ibuprofen was from The Boots Pure Drug Co., Nottingham, U.K. Transcutol (purified diethylene glycol monoethyl ether) was a gift from Gattefosse Etablissements, Saint-Priest, France. Sur-

factants of the Brij series were supplied by ICI Speciality Chemicals Ltd. All other chemicals used were of at least Analar grade.

Human male and female abdominal or female breast skin was obtained either at post-mortem or from cosmetic reduction surgery. Subcutaneous fat was removed by blunt dissection prior to use. The thickness of the prepared epidermal membranes (full thickness skin) was measured with a micrometer and the membranes were subsequently placed between the two halves of horizontal Franz-type glass diffusion cells, the stratum corneum facing the donor chamber. The cells were designed such that the area available for diffusion was about 0.8 cm^2 (range 0.65–0.92 cm^2), the exact area being measured for each diffusion cell. Receptor chamber volume varied from 2.1 to 2.4 ml, the exact volume being measured for each diffusion cell. The diffusion cells were immersed in a constant temperature water bath such that the receptor chambers were kept at 37.0 ± 0.5°C throughout the experiment. This ensured that the skin surface temperature was maintained at 32.0 ± 1°C. The receptor chamber contents were continuously agitated by small PTFE-coated magnetic followers driven by submersible magnetic stirrers.

The receptor chambers of the diffusion cells were filled with a known volume of pH 7.4 phosphate-buffered saline containing 25% ethanol, capped, and allowed to equilibrate to the correct temperature.

Approx. 500 μl, accurately measured, aliquots of the test media were applied to the skin surface. Various vehicles containing ibuprofen (at 5% w/v) were applied to the donor chamber and 200 μl samples taken from the receptor medium at intervals up to 48 h and the liquid replaced by fresh receptor medium. The samples were subjected to analysis by HPLC. A total of seven replicates were used for each dosage regimen.

HPLC separation was conducted on a μBondapak C18 column (Waters), 25 cm × 4.6 mm using the mobile phase: methanol/0.25% aqueous glacial acetic acid (70:30) at ambient temperature, a Rheodyne 7125 injector with 20 μl loop, LDC CM4000 pump, SM4000 detector at 263 nm and CI4100 integrator. There was no interference from other compounds in the receptor phase solutions from blank skin samples maintained under the same experimental conditions.

Results

There was no significant correlation between the penetration of ibuprofen and thickness of male skin, particularly over prolonged periods (Fig. 1). Nevertheless, it appeared that the largest variations in the rate of penetration occurred using thinner membranes. Penetration rates for hairless and pellaged skin were similar, but in this case there was greater variability (SD 65%) compared with non-hairy skin (SD 25%). Further experiments were conducted using female skin which was almost completely hairless.

Application of ibuprofen dissolved in transcutol did not produce any measurable flux. On addition of water to form a binary solvent system the penetration of ibuprofen increased as a function of the volume fraction of water (Fig. 2). 5% ibuprofen is not completely soluble in the 1:1 transcutol-water system at 30°C. At 60% water, therefore, some ibuprofen was in suspension. Despite this, penetration of the drug was significantly increased. Fig. 3 illustrates the influence of

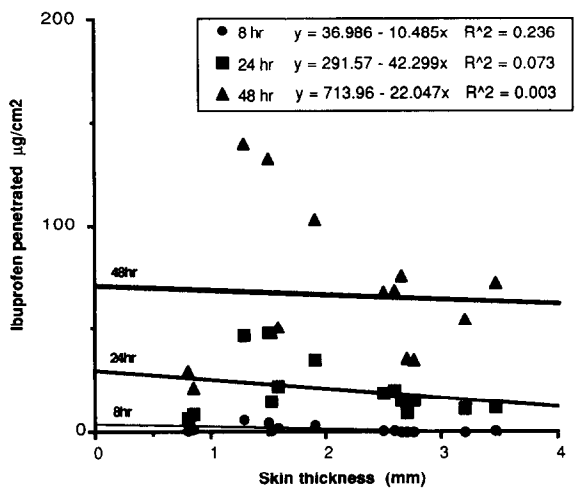

Fig. 1. Correlation between skin permeation of ibuprofen and thickness for human male skin.

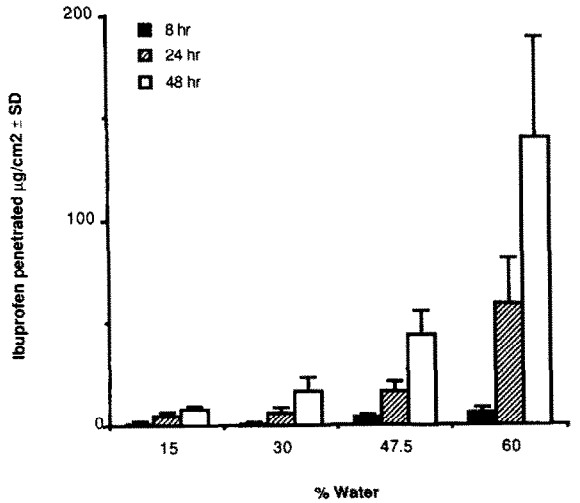

Fig. 2. Ibuprofen penetration through human female skin as a function of water content in transcutol-water binary systems (ibuprofen concentration 5% w/w).

type and concentration of polyoxyethylene (POE) alkyl ethers of the Brij 90 series which are based on an oleyl alkyl chain and possess varying oxyethylene chain lengths. 1% oleic acid increased the rate of penetration of ibuprofen 1.36-fold. Using POE[2]oleyl ether (Brij 92) maximal flux was observed when 2% of the surfactant was included (enhancement factor 3.42). Increase in Brij 92 concentrations up to 5% decreased the flux, but it remained higher than that obtained

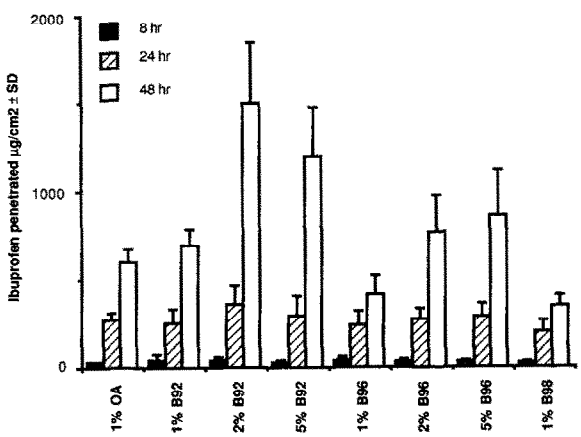

Fig. 3. Ibuprofen penetration through human female skin from 1:1 transcutol-water systems as a function of type and concentration of adjuvant (ibuprofen concentration 5% w/w). OA, oleic acid; B92, Brij 92; B96, Brij 96; B98, Brij 98.

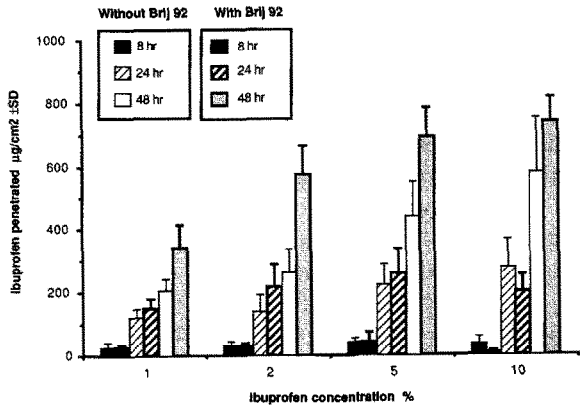

Fig. 4. Ibuprofen penetration through human female skin from 1:1 transcutol-water systems as a function of ibuprofen concentration.

with no surfactant. Brij 92 is poorly soluble in 1:1 transcutol-water solution and the 2 and 5% systems were cloudy. Brij 96 (POE[10]oleyl ether) was soluble in the concentration range investigated and the rate of penetration increased with increase in surfactant concentration above 1%. The most hydrophilic surfactant Brij 98 (POE[20]oleyl ether) at 1% reduced the rate of penetration of ibuprofen (enhancement factor 0.79).

A fixed concentration (1% w/v) of Brij 92 was used to investigate the effect of different ibuprofen concentrations on penetration (Fig. 4). As would be expected, the amounts of ibuprofen permeated increased with increasing concentration of ibuprofen in the donor phase. Addition of 1% Brij 92 considerably increased ibuprofen permeation at all ibuprofen concentrations.

Discussion

It is generally accepted that in the case of very hydrophobic compounds the stratum corneum is not the only barrier to percutaneous absorption (Bronaugh and Stewart, 1984). The permeation of a compound can be affected by skin appendages (Schaefer et al., 1990; Wepierre et al., 1990) and the thickness of the skin layers beneath the stratum corneum (Bronaugh et al., 1986a,b). In the case of ibuprofen, where water solubility is very

low, the thickness of the skin was not expected to play any significant role in altering the rate of penetration. Nevertheless, it is apparent from Fig. 1 that there were large differences between skin samples. As a consequence the average amount of ibuprofen permeating over 48 h was 613 ± 326 $\mu g/cm^2$ for male skin and 439 ± 114 $\mu g/cm^2$ for female skin. The higher variability with male skin correlated with a greater density of hair follicles and provided an explanation for difficulties in the evaluation of the data in the previous report (Bialik et al., 1991). The use of female whole skin generated more reproducible results and permitted effective assesment of the influence of vehicle components.

A primary factor governing penetration phenomena is the ability of the penetrant to partition out of the delivery vehicle and into the upper layers of the stratum corneum. It is possible, therefore, to increase the skin permeation rate by manipulation of the vehicle to increase the thermodynamic activity of the dissolved permeant (Fig. 2). Ibuprofen is readily soluble in transcutol and the escaping tendency is low. Addition of water in which ibuprofen is less soluble increases the thermodynamic activity with consequent increase of the skin permeation rate. When the volume fraction of water is very high more of the drug precipitates causing a substantial decrease of solute concentration. However the further increase in escaping tendency produces more rapid penetration and the undissolved drug provides a reservoir ensuring solution saturation with the permeant throughout the experiment.

Penetration through the skin can be modified by surfactants which can penetrate and interact with the skin. Interaction of surfactant with the permeant (e.g., micellar solubilisation) can also occur. Therefore, a surfactant can either increase, decrease, or have no effect on skin absorption (Walters, 1990). The data given in Fig. 3 shows that all these cases occurred. Brij 92 increased the rate of penetration at all concentrations. In the case of Brij 96 acceleration of permeation was only found at higher concentrations. Brij 98 acted as a penetration inhibitor at 1% concentration. The most likely explanation for these phenomena is that shorter ethylene oxide chain surfactants possess a greater affinity for the intercellular multilamellar lipid phases of the stratum corneum. This results in increased fluidity in this region which presumably reduces diffusional resistance. There is evidence that the fluidity of lipid monolayers (Walters et al., 1982) and bilayers (French et al., 1990) can be increased when polyoxyethylene alkyl ethers are incorporated.

From Fig. 4 it is clear that, for a completely saturated system (10% ibuprofen), addition of surfactant only slightly increased the rate of penetration. A more significant effect was observed in the case of an unsaturated system (5% ibuprofen) with the greatest enhancement occurring with a 2% ibuprofen solution. From a practical point of view it is important to stress that the total amounts of ibuprofen penetrating over 48 h were almost the same in each of these cases. This makes it possible to reduce the dose of ibuprofen without a significant decrease in the penetration rate. At the 1% level it is possible that the solubilizing capacity of Brij 92 was predominant, reducing the thermodynamic activity of ibuprofen, although, because of the reduction of the diffusion barrier of the skin, the total effect was positive.

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