The Penetration Enhancement Effect of Single and Binary Phase Combinations of Hydrophilic and Lipophilic Vehicles, Using Ibuprofen as a Model Drug

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ABSTRACT SUMMARY

The aim of this study was to determine the penetration enhancement effects of different penetration enhancer vehicles on the permeation of lipophilic ibuprofen through synthetic Carbosil® membrane, when used individually and in multi-component solvent mixtures during Franz cell diffusion.

Water and propylene glycol, as well as mineral oil and Miglyol® was used as penetration enhancer vehicles in combinations of 0/100 (v/v), 20/80 (v/v), 50/50 (v/v), 80/20 (v/v) and 100/0 (v/v) at different infinite volumes (250 µl, 500 µl and 1 000 µl).

INTRODUCTION

Transdermal drug delivery has the advantage over other routes of administration of avoiding the hepatic, first-pass metabolism that would result in better therapeutic efficacy, better patient medication compliance and reduced systemic side-effects1. One disadvantage of this mode of drug delivery is the generally poor delivery of drugs through the skin. The intercellular lipid structure of the stratum corneum causes this membrane to be an excellent penetration barrier, which must be breached to enhance drug penetration through the skin.

The synthetic membrane, Carbosil®, a polydimethylsiloxane-polycarbonate (PDMS-PC) block copolymer, was used to mimic the barrier function of the stratum corneum. As for human skin epidermis, this synthetic membrane has a heterophasic and heteropolar structure and shares a common solubility-diffusion mechanism of drug transport, which provides a mechanically substantiated model for transdermal drug absorption2.

Factors influencing the drug-skin distribution include the physicochemical properties of the drug, the choice of the delivery vehicle and the drug application mode (finite and infinite dose) being used3. The permeability of the skin is thus influenced by the physicochemical properties of both the permeant and the penetration enhancer4.

Chemical penetration enhancers use different mechanisms of action to increase permeation across the skin5. When chemical enhancers are used in combination, a synergistic action between these enhancers offers a method of overcoming limitations being experienced when single chemical enhancers are used in improving transdermal drug delivery6.

EXPERIMENTAL METHODS

Twenty four glass vertical Franz diffusion cells with a receptor capacity of approximately 2 ml and diffusion area of 1.075 cm² were used. Carbosil® membrane (pre-soaked) was cut into circles in order to cover the diffusion area of the Franz cell. The membranes were placed on the receptor compartment of the Franz diffusion cell with the donor compartments placed on top. Thereafter, it was sealed with Dow-corning® vacuum grease and clamped with metal horseshoe clamps. A small magnetic stirrer bar was placed in each receptor compartment.

PBS (pH 7.4 at 37 °C) was used to fill the receptor compartment and care was taken not to allow bubbles to form. The diffusion cells were placed in a tray on a Variomag® stirrer plate in order to continuously stir the receptor phase inside a Grant® water bath at 32 °C, simulating the temperature of human skin7.

An hour before the experiment commenced; saturated solutions (32 °C) of ibuprofen in the different solvents or combination of solvent vehicles were prepared. Depending on the experiment conducted a specific volume of saturated solution was applied to the membrane. The volumes that were tested were as follow: 250, 500 and 1 000 µl.

RESULTS AND DISCUSSION

The binary penetration enhancement solvents containing mineral oil and Miglyol®, showed the best diffusion enhancement effects for ibuprofen. The 20/80 (v/v) mixture of mineral oil/Miglyol® increased the permeation of ibuprofen through the Carbosil® membrane to the highest level than any of the other vehicles of both groups, tested. This would have been due to the synergistic action of the two solvents.

The penetration enhancement effect of propylene glycol increased as the percentage of the propylene glycol in a combination solvent vehicle increased, and as the application volume of a single phase vehicle increased. Its mechanism of action is to partition into the stratum corneum and to increase the solubility of the permeant in the membrane, causing an increase in the flux of both the propylene glycol and the permeant5. As Carbosil® membrane shares the same heteropolar structure as human stratum corneum; the same mechanism of action is applicable to the Carbosil® membrane.
CONCLUSION

The outcomes of this study further showed that the single and multi-component solvents containing water, delivered less of the active through the Carbosil® membrane, compared to the other solvents tested. Contrary to water, mineral oil and Miglyol®, propylene glycol individually showed good penetration enhancement properties.

The penetration enhancement potential of the four chemicals used in this study individually or in combination, was investigated in an attempt to identify chemicals that could in future be successfully employed for facilitating delivery of drugs through the human skin barrier. The results from this study confirmed the observations by Williams & Barry:

a) Penetration enhancer properties appear to be drug specific (permeants with similar physicochemical properties).
b) Penetration enhancers tend to work well with co-solvents, such as propylene glycol.
c) Most penetration enhancers have a complex concentration dependent effect.
d) Potential mechanisms of action of penetration enhancer solvents are different, and can range from direct effects on the skin to modification of the formulation.

REFERENCES


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