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Factors affecting the permeation of urea and water through nude mouse skin in vitro: IV. Polymer carriers

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Summary

The influence of polymer carriers on the permeation of water and urea through nude mouse skin in vitro was investigated. The permeation was followed in an open diffusion cell system using labelled water and urea. The permeability profiles for JR 125, JR 400, JR 30M, GAF 734 and GAF 755N polymers and a control sample were obtained. It was found that the different cationic polymers affected the permeability coefficient of water and urea differently. The role played by the type of polymer depends on the physico-chemical properties of the polymer and the diffusant, respectively.

Introduction

The major difference between drugs administered systemically and those applied topically is the greater role played by the vehicle. While excipients in the formulation of oral tablets or capsules can affect bioavailability patterns, these effects are minor when compared to the material influence topical vehicles can exert upon the release of drugs to the skin (Idson, 1983). Studies concerning the effect of vehicles on the percutaneous absorption of substances have been reviewed by many authors (Barry, 1983; Idson, 1983; Wester and Maibach, 1983; Lippold, 1984; Zatz, 1985).

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The vehicle is of subsidiary importance if the factor influencing percutaneous absorption is the passage of the diffusant itself through the skin (Ritschel and Hussain, 1987). The percutaneous absorption may, however, be influenced if diffusion of a substance from a vehicle is retarded. In polymer solutions the structural and chemical properties of the polymer control diffusion and may alter any diffusional process (Cooper, 1985). The objective of this study was to determine whether cationic polymer vehicles would affect the percutaneous absorption of substances such as water and urea.

Due to the factors exerted on a diffusant by the vehicle it is impossible to design a vehicle which is universally acceptable. An optimal vehicle for one agent may be nearly worthless for another of which the general physico-chemical properties are different (Idson, 1983). An optimal vehicle must therefore be designed for each drug (Katz and

Poulsen, 1972), and polymers have been shown to have great potential in this field (Drobnik and Rypnacek, 1984).

Materials and Methods

Materials

The following materials were used as received from the suppliers: Polymers JR 125, 400 and 30 M with average molecular weights of 250 000, 400 000 and 600 000, respectively (supplied as a white powder); Gafquat copolymer 734, with an average molecular weight of 100 000, supplied as a 50% viscous alcoholic solution; Gafquat copolymer 755N, with an average molecular weight of 1×10^6, supplied as a 20% viscous aqueous solution; [^{14}C]urea (spec. act. 250 μCi/mg; supplied as a freeze-dried solid); [^{3}H]water (spec. act. 1 Ci/ml); de-ionized water; unlabelled urea (analytical grade) and sodium chloride injection BP 0.9% (w/v) (normal saline).

Methods

Mouse skin preparations

The dorsal skins of male nude mice were used exclusively in this study. Two adult mice approx. 3 months of age with a weight of 27.2 g were used.

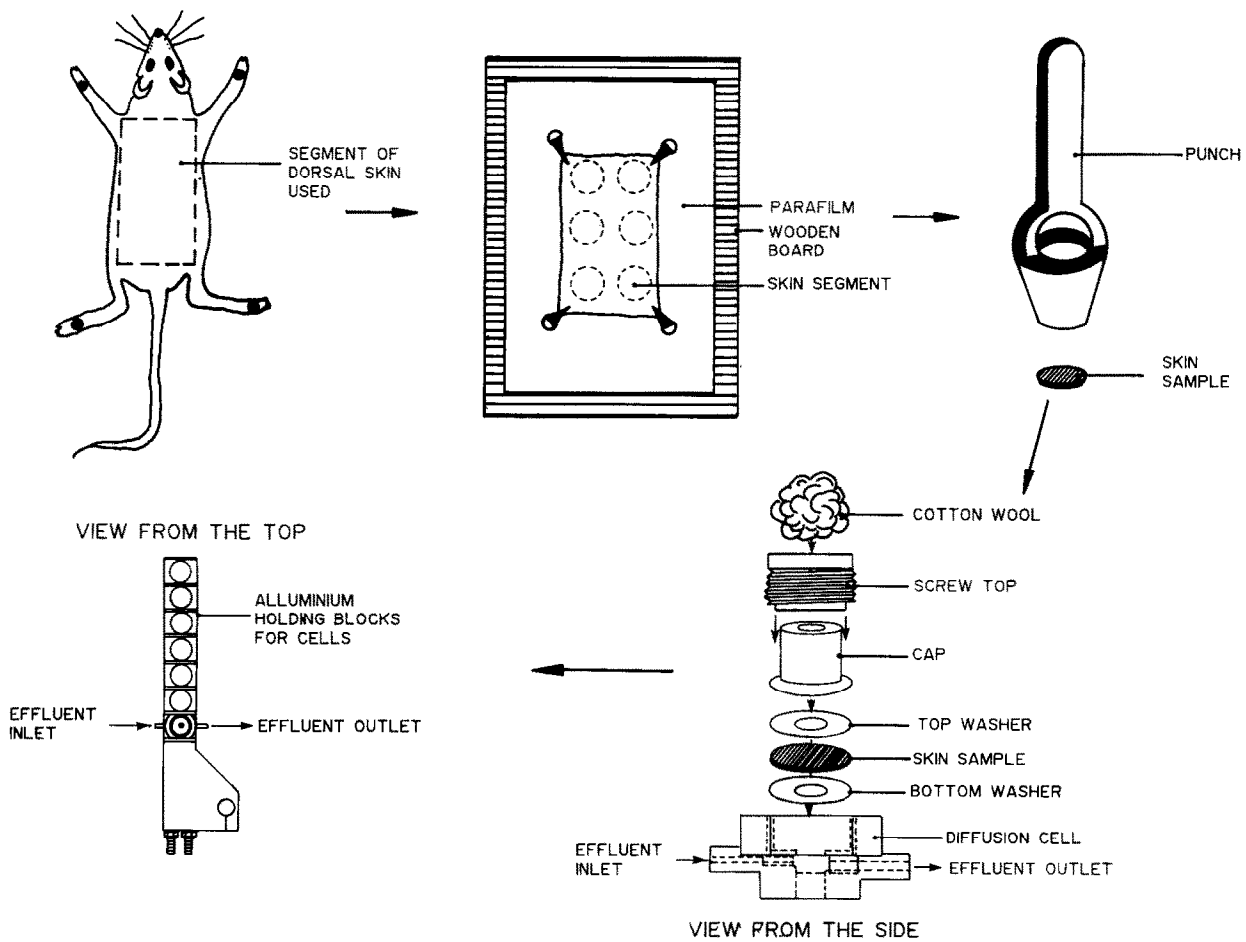

Fig. 1. Schematic diagram of the preparation of hairless mouse dorsal skin segments for the experiments conducted with the open-cell diffusion system.

The mice were killed by inhalation of carbon dioxide. Full-thickness dorsal skin (5 cm^2) was removed from each mouse by blunt dissection. The necessary precaution was taken during preparation to ensure that the skin was not subjected to any stretching or strain that could damage it. All skin samples were treated as shown in Fig. 1.

A sheet of parafilm was stapled to a wooden board. The skin, with the dermis side upwards, was spread evenly onto the parafilm sheet. The skin was secured in the corners with pins to prevent curling. Excess fatty tissue was carefully removed from the dermis side of the skin with a scalpel and tweezer. Four to seven round segments, 1.6 cm in diameter, were punched from the skin with a circular punch.

Teflon washers (0.64 cm i.d. × 1.60 cm o.d. × 0.05 cm thick) were punched from the teflon sheet. Each skin segment was placed on a round teflon washer with the dermis side of the segment towards the washer. A second teflon washer was placed onto the stratum corneum side of the segment so that the center hole of each of the teflon washers on either side of the segment was exactly opposite the other. A prepared segment was placed into each of the seven diffusion cells (Fig. 1), with the stratum corneum side facing upward. A minimum of three segments from each of the two mice were used for the seven diffusion cells. The segments were secured in the diffusion cell with a screw top.

Preparation of stock solutions

All stock solutions were prepared from the materials as received from the suppliers. These procedures were performed by using Finnpipettes and Eppendorf comfortips. The stock solutions were used as prepared. Where normal saline was used as solvent it provided isotonic solutions.

Solutions of 1 and 2% (w/v) of each of the three grades of polymer (JR 125, 400 and 30M) were freshly made up. At each concentration three solvents were used, namely: (1) 0.06% (w/v) urea in normal saline, (2) normal saline and (3) deionized water. The solvents were preheated to 45 °C to facilitate solubility of the polymer.

The 1 and 2% (w/v) solutions of the Gafquat 734 polymer were prepared by adding 2 and 4 ml of the viscous alcoholic solution to 98 and 96 ml of each of the above-mentioned solvents, respectively. The volumes were corrected after cooling. Clear solutions resulted.

The 1 and 2% (w/v) solutions of the Gafquat 755N polymer were prepared by adding 5 and 10 ml of the viscous aqueous solution to 95 and 90 ml of each of the solvents, respectively. Clear solutions resulted.

The [^{14}C]urea solution was made up by diluting the freeze-dried solid to 5 ml with ethanol. The [^{3}H]water solution was made up by adding 10 ml of the original solution to 9990 ml of ethanol. 1000 ml of this solution was diluted to a 5 ml secondary solution with ethanol. The 0.06% (w/v) urea solution was prepared by dissolving 1,212 g of the urea to 2000 ml of normal saline. The 1.20% (w/v) urea solution was prepared by dissolving 0.242 g of the urea to 200 ml of normal saline. The polymer and urea solutions were freshly prepared before each experiment. The polymer/labelled mixtures used during these studies were made up from the prepared stock solutions as follows:

2% polymer solution	500
[^{3}H]water	150
[^{14}C]urea	300
1.20% (w/v) urea	50
Total	1000

The polymer solution resulted as a 1% (w/v) solution in the polymer/labelled mixtures. The 1.20% (w/v) urea solution resulted as a 0.06% (w/v) solution in the polymer/labelled mixture.

Calculation of the permeability coefficient

The following equation was used:

$$P = V(dc/dt)/A(C_0 - C_x)$$

where P denotes the permeability coefficient (cm/h), V is the volume of the receptor fluid at the time interval (x), dc/dt represents the steady-state slope (dpm/cm^3 per h), A is the diffusional area of the diffusion cell (0.32 cm^2) and $C_0 - C_x$ corresponds to concentration difference across the membrane, which was calculated by subtracting the cumulative receiver phase

concentration at time interval x (cpm/cm^3) from the concentration of the donor phase prior to the study (C_0).

Results and Discussion

The combined profiles of the permeability coefficients as a function of time for water and urea with the JR polymers and the Gafquat polymers are represented in Figs. 2 and 3, respectively.

Water

The permeability profiles observed for water showed no significant difference ($p < 0.05$) in the percutaneous absorption of water between the control and that of GAF 734 up to 5 h. A lower permeability was observed with the GAF 755N polymer up to 5 h. A significant difference ($p < 0.05$) was observed between the control and the GAF 734 and GAF 755N polymers after 5 h. The GAF 734 and 755N polymers had a higher pseudo steady state than the control.

The observed percutaneous absorption profiles of water with the Gafquat polymers resembled those obtained with the JR polymers. The differences observed up to 5 h may be the result of the individual average molecular weight and cationic nature of each polymer. The chemical structure of the polymers probably played a secondary part in the percutaneous absorption of water with these polymers. The chemical structure influences the coiling tendencies of the polymers and this may have altered the diffusivity of water inside the polymer network. Differences in diffusivity will be reflected in the pseudo steady-state permeability coefficients if it is assumed that the polymer forms the rate-limiting phase for the diffusion of water in this type of experiment. Both polymers (GAF 734 and GAF 755N) enhanced the percutaneous absorption of water significantly ($p < 0.05$) when compared to the control, with the higher molecular weight polymer (GAF 755N) being the better penetration enhancer of the two polymers. GAF 755N may have an increased hydration effect on the skin, which increases the diffusivity of water in the skin and consequently leads to a higher permeability coefficient in the pseudo steady-state phase. Other factors such as an increased viscosity, substantivity, surface activity and cationic na-

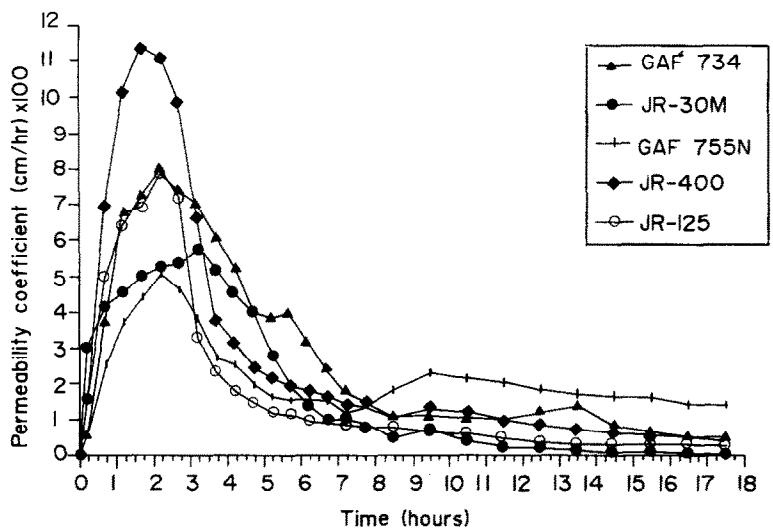

Fig. 2. The permeability coefficient as a function of time for the percutaneous absorption of [^{3}H]water from normal saline and polymer solutions.

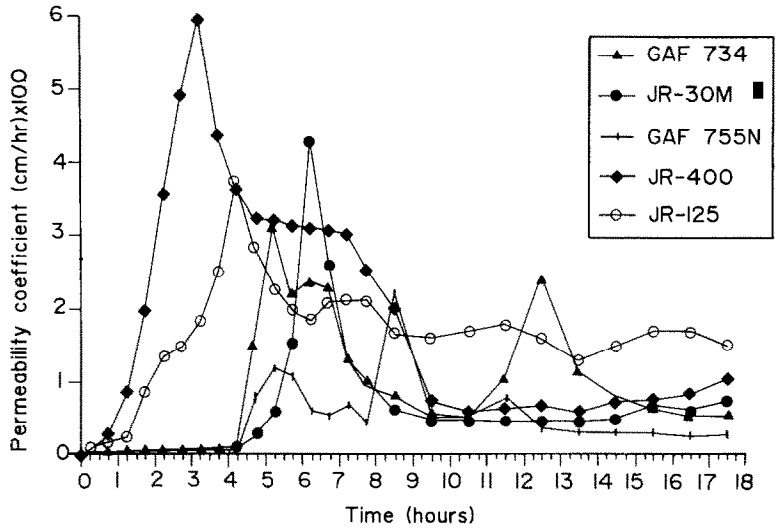

Fig. 3. The permeability coefficient as a function of time for the percutaneous absorption of [^{14}C]urea from normal saline and polymer solutions.

ture, which may all be related to molecular weight, could cause the different permeability coefficients observed in the pseudo steady-state phase.

Urea

The permeability profiles of urea for the Gafquat polymers showed little resemblance to that obtained for the JR polymers (Fig. 3). The permeation profiles of the two Gafquat polymers were much lower than the control and presented significantly different ($p < 0.05$) patterns up to 15 hours.

The Gafquat polymers had a significant ($p < 0.05$) influence on the permeation profiles of urea. A lag time of 4.3 h was observed for both GAF 734 and 755N before the typical shunt diffusion peaks appeared. A possible explanation for the lag time might be that the smaller and more densely packed coils of GAF 734 and GAF 755N than those of the JR polymers might block the diffusional pathways used by urea for shunt diffusion. The urea had to overcome this barrier before shunt diffusion occurred. The shunt diffusion and following pseudo steady state of both the GAF polymers followed the same pattern as obtained with the JR polymers in that the cationic nature of the polymers lowered the barrier properties of the stratum corneum by penetrating it to a certain extent. The lower percutaneous profiles observed might be the result of the barrier properties of the GAF 734 and GAF 755N polymer coils to the diffusion of the urea from these polymer solutions. A second increase in permeability for GAF 734 and GAF 755N appeared after 12 and 8 h, respectively. An explanation might be the rearrangement of the coils of the polymers influencing the rate of diffusion of urea from the polymers.

It may be concluded that different cationic polymers affect the permeability coefficients of water and urea differently. The role played by the type of polymer will depend on the physico-chemical properties of the polymer and the diffusant, respectively.

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