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White Paper

Permeation of ketoprofen, diclofenac diethylamine and diclofenac sodium formulated in AKVANO® vehicles, compared to commercial products using artificial membranes

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Summary

In vitro permeation experiments using Strat-M® membranes were performed on ketoprofen, diclofenac diethylamine and diclofenac sodium formulations in AKVANO®, a drug delivery technology based on lipid components dissolved in a volatile solvent mixture. The results show that by selecting lipids with barrier strengthening properties it is possible to reduce the permeation rate. A moderate amount of penetration enhancing lipids will increase the flux but still result in a prolonged release profile, whereas with a higher amount of the penetration enhancing lipids, the formulations give faster or equally fast permeation compared to the commercial products Orudis® gel (2.5 % ketoprofen) and Voltaren® gel (2.3 % diclofenac diethylamine).

Introduction

Studies in dermatopharmacokinetics by *in vitro* testing in diffusion cells is a well-established field, and have been used for assessing vehicle effects in drug formulation[1,2]. The classical equipment for these studies is the Franz cell, which is a static set-up with two chambers (donor and receptor) separated by a membrane, through which the permeation of the substance of interest is studied by measuring the accumulated concentration in the donor compartment. The membrane can be excised skin from humans or animals or artificial membranes which mimic the behavior of the skin. Strat-M® membranes is a recently developed type of artificial membranes which have shown to give a fair prediction of skin permeation[3].

An alternative to the Franz cell is to use flow-through cells, which allow continuous sampling of the receptor fluid, and in this case measures the differential of the permeation curve. The two types of equipment have been shown to be in satisfactory agreement in their results[4].

AKVANO® is a drug delivery technology based on sprayable formulations consisting of lipid components dissolved in a volatile, water-free solvent mixture. When this formulation is applied onto the skin, the solvent evaporates and a non-occlusive lipid layer is formed in an immediate interaction with the skin surface. Earlier studies show that by choosing different lipids in the AKVANO vehicle the skin barrier could either be strengthened or weakened, manifested by changes in transepidermal water loss (TEWL)[5].

In this study we have used an equipment where Strat-M® membranes in eight flow-through cells are run in parallel to study the permeation of ketoprofen, diclofenac diethylamine and diclofenac sodium in AKVANO formulations, and also in commercially available medicaments.

Materials and methods

Three different types of AKVANO vehicles were used in the study. AKVANO A consists only of barrier strenghtening lipids while AKVANO B and AKVANO C also contains different levels of penetration enhancing lipids. A formulation of ketoprofen in AKVANO B was compared to Orudis® gel (2.5 % ketoprofen), while formulations of diclofenac diethylamine in AKVANO A, B and C were compared to Voltaren® gel (2.3 % diclofenac diethylamine). Finally, diclofenac sodium was tested in AKVANO A, B and C.

Experiments using the same type of equipment as in this study have been reported previously[6]. In short, the system consists of a buffer reservoir containing PBS buffer pH 7.4, an 8-channel peristaltic pump, eight flow-through diffusion cells with a cross section area of 0.5 cm^2 placed on a stainless steel platform which is kept at 37 °C, and an 8-channel fraction collector. The buffer is transported in the system through Teflon tubes (0.5 mm ID).

A Strat-M® membrane of appropriate size was placed between the donor chamber and the receiving chamber. The flow rate was adjusted to approximately 1.5 ml/h. Approximately 5 mg of formulation was applied on top of the membranes. The top of the donor chamber was left open in order to allow evaporation of the volatile solvent. Fractions of the receptor fluid were collected during 0-2, 2-4, 4-6, 6-10, 10-14, 14-18 and 18-24 hours. The concentration in the receptor fluid was analyzed by RP-HPLC with UV detection (240 nm for ketoprofen and 274 nm for diclofenac salts).

The remaining amount of active substance in the membranes was analyzed after extraction with 1 ml of methanol overnight.

Results

In the first experiment the ketoprofen/AKVANO B formulation and Orudis gel were compared using four cells each. One of the Orudis cells were not included in the analysis due to several interruptions of the flow. The flux J (µg/h) was calculated according to Equation 1:

$$J_i = C_i V_i / t_i \qquad \text{(Eq. 1)}$$

Where i is the fraction number, C_i is the concentration in µg/ml, V_i is the volume of the fraction (ml) and t_i is the time in hours during which the fraction was collected. The cumulative permeation Q was calculated according to Equation 2:

$$Q_n = \sum_{i=0}^{n} J_i t_i / m_{nom} \qquad \text{(Eq. 2)}$$

Where m_{nom} is the nominal amount of active substance in µg added to the membrane at the start of the experiment.

The results from the ketoprofen experiment is shown in Figures 1-3. The charts demonstrate a much faster permeation profile for the ketoprofen/AKVANO B formulation than for Orudis gel. A significant part of the initial content of ketoprofen in Orudis gel is retained on the membrane, whereas for AKVANO B the retained amount is negligible.

In three subsequent experiments the permeation of diclofenac diethylamine in AKVANO A, B and C were compared with Voltaren gel. Also during these experiments there were disturbances in the flow and the results from 3 of 24 cells had to be disregarded. The combined results are presented in Figures 4-6 and show that the AKVANO A formulation gives a slow release of diclofenac diethylamine, whereas the AKVANO B and C formulations give faster permeation, and the AKVANO C formulation even faster than Voltaren gel, though the difference is not statistically significant. For all four formulations a portion of initially applied diclofenac diethylamine is retained on the membrane but the differences between formulations are not statistically significant.

In a final set of experiments AKVANO formulations of diclofenac sodium were tested. The results, presented in Fig. 7-9, show a similar trend as for diclofenac diethylamine, though the permeation rate is generally slower. It can also be seen that the amount retained on the membrane is higher for the AKVANO A formulation than for AKVANO B and C formulations.

Conclusion

The experiments show that the by adjusting the composition of lipid components in AKVANO vehicles, it is possible to control the permeation through Strat-M membranes. By using a lipid composition with only barrier strengthening components, the penetration is relatively slow, and a significant part of the active substance is retained in or on the membrane. With a moderate amount of penetration enhancing lipids, the flux is increasing but show a prolonged release profile. Finally with a higher amount of the penetration enhancing lipids, the formulation gives faster or equally fast release of the active substance through the membrane compared to the commercial products.

Fig. 1 Flux of ketoprofen through Strat-M® membranes

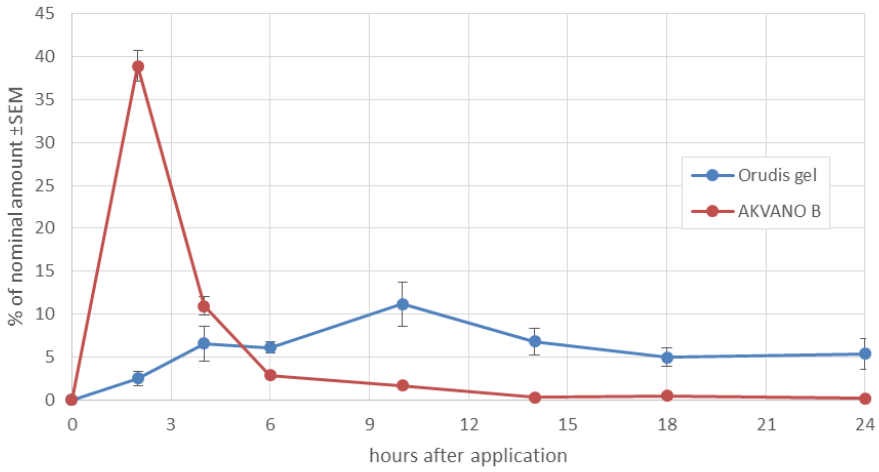


Fig 2. Cumulative permeation of ketoprofen through Strat-M® membranes

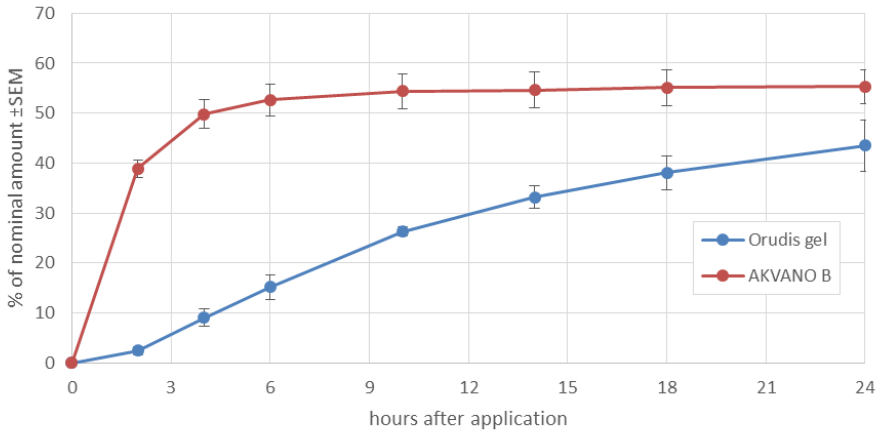


Fig. 3 Ketoprofen remaining in Strat-M® membranes

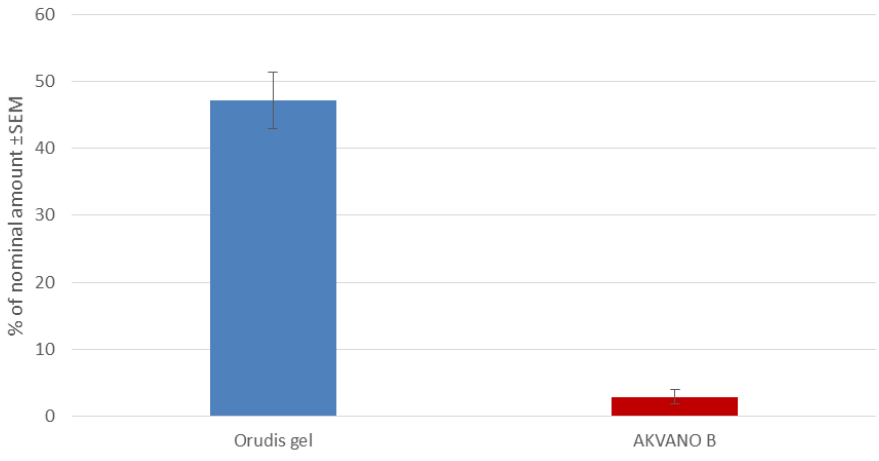


Fig. 4 Flux of diclofenac diethylamine through Strat-M® membranes

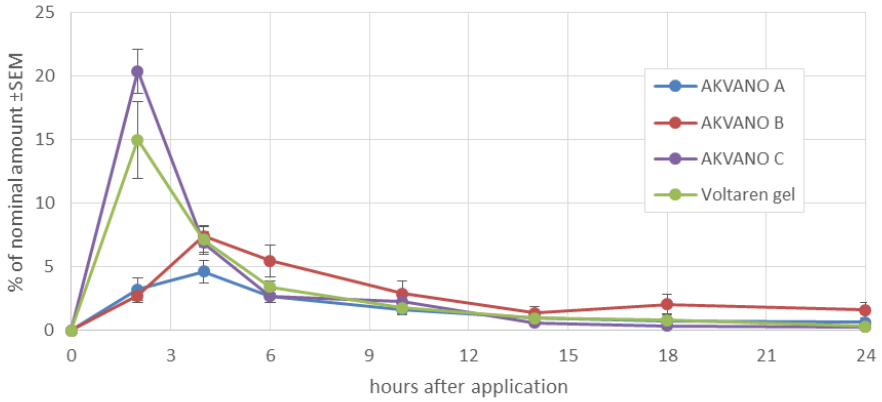


Fig 5. Cumulative permeation of diclofenac diethylamine through Strat-M® membranes

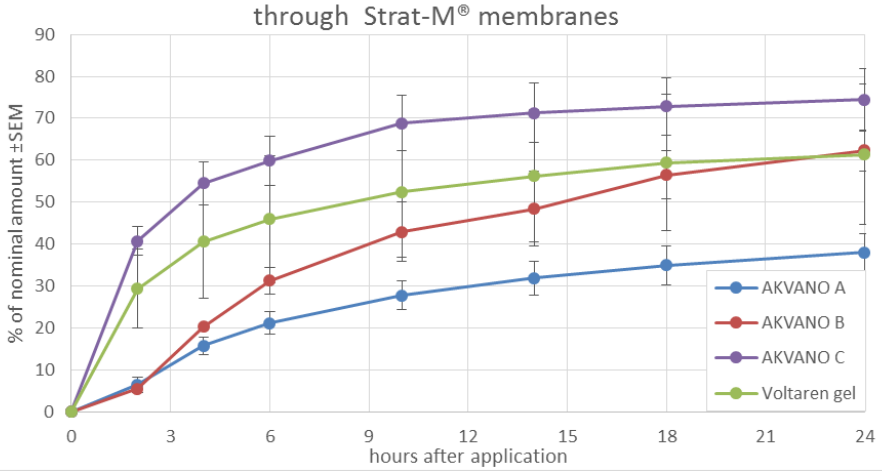


Fig. 6 Diclofenac diethylamine remaining in Strat-M® membranes

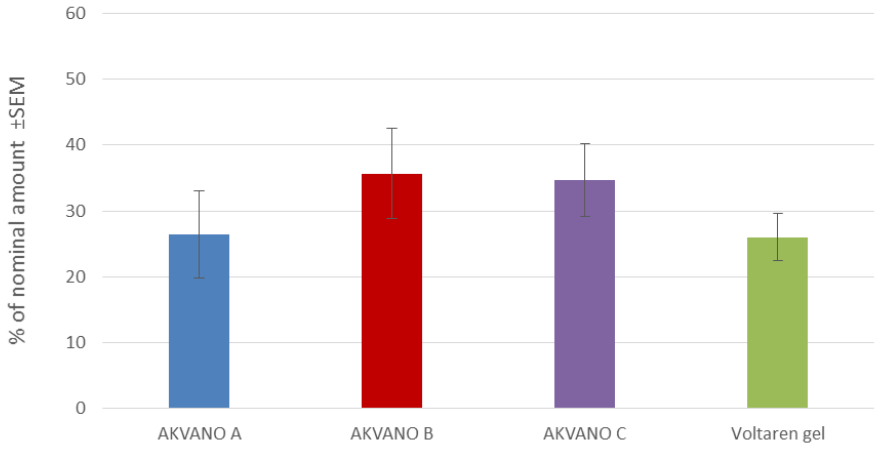


Fig. 7 Flux of diclofenac sodium through Strat-M® membranes

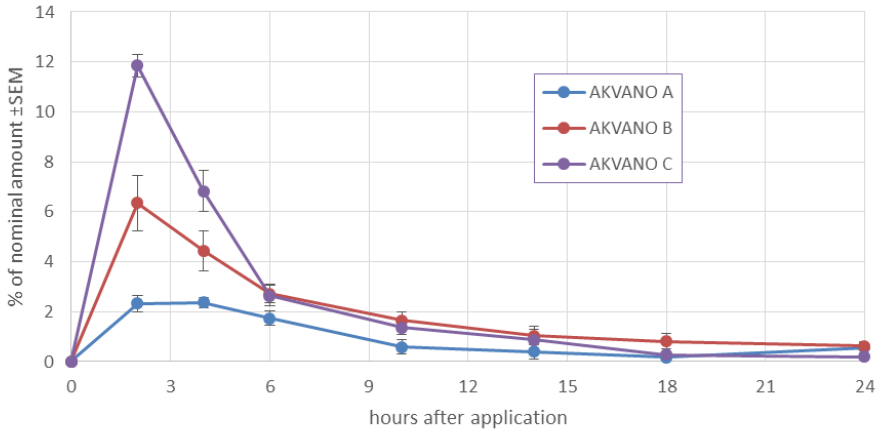


Fig. 8 Cumulative permeation of diclofenac sodium through Strat-M® membranes

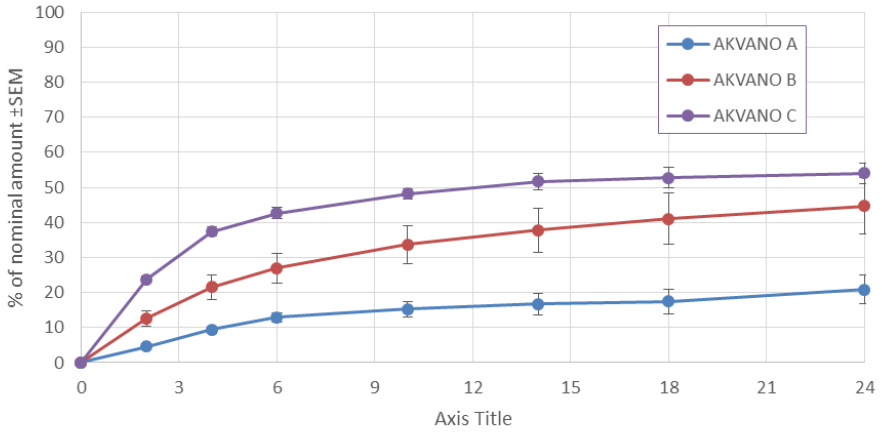
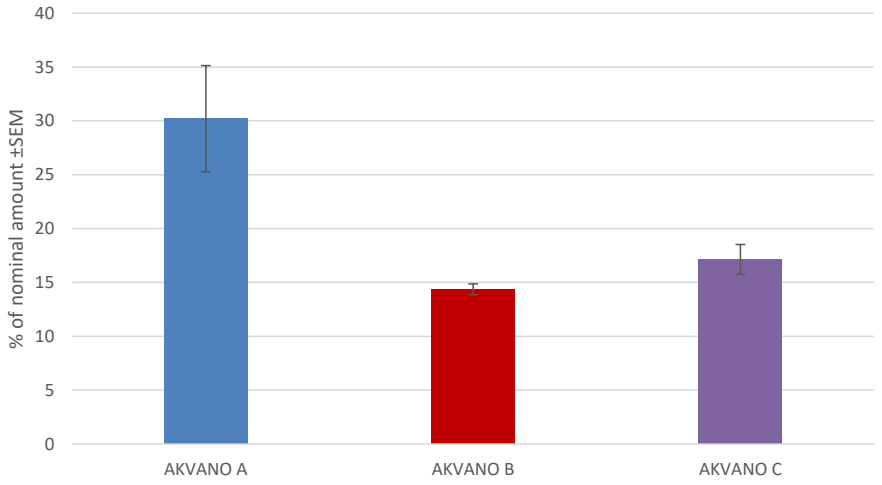


Fig. 9 Diclofenac sodium remaining in Strat-M® membranes



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