Dermal absorption of chemicals through normal and compromised skin
Jakasa, Y.

Citation for published version (APA):

General rights
It is not permitted to download or to forward/distribute the text or part of it without the consent of the author(s) and/or copyright holder(s), other than for strictly personal, individual use, unless the work is under an open content license (like Creative Commons).

Disclaimer/Complaints regulations
If you believe that digital publication of certain material infringes any of your rights or (privacy) interests, please let the Library know, stating your reasons. In case of a legitimate complaint, the Library will make the material inaccessible and/or remove it from the website. Please Ask the Library: http://uba.uva.nl/en/contact, or a letter to: Library of the University of Amsterdam, Secretariat, Singel 425, 1012 WP Amsterdam, The Netherlands. You will be contacted as soon as possible.
Chapter 4: Section 4.2

Altered penetration of polyethylene glycols into uninvolved skin of atopic dermatitis patients
I. Jakasa, M.M. Verberk, M. Esposito, J.D. Bos, S. Kezic
(submitted to J Invest Dermatol)
Abstract

Involved regions of the skin in atopic dermatitis patients have an altered barrier function. Whether uninvolved skin also has a diminished barrier is controversial. To assess the barrier function of uninvolved skin in atopic dermatitis patients, the percutaneous penetration of polyethylene glycols of various molecular sizes was determined in atopic dermatitis patients and control subjects. The percutaneous penetration was assessed using tape stripping of the stratum corneum. The diffusion coefficient and stratum corneum/vehicle partition coefficient were determined using Fick's second law of diffusion. The stratum corneum thickness was similar in both groups, however, the transepidermal water loss was higher in atopic skin. The diffusion coefficient of polyethylene glycols through atopic skin was twice as high as through normal skin, and decreased with increasing molecular weight in both groups. The partition coefficient in the skin of atopic dermatitis patients was half of that for normal skin but as for normal skin there was no molecular weight dependency. Although atopic skin exhibited altered barrier with respect to diffusion coefficient and partitioning, the permeability coefficient, were nearly the same for atopic and normal skin. The results support the hypothesis of altered skin barrier of AD patients even in the skin that is visibly unaffected by disease.
Chapter 4: Section 4.2

Introduction

The affected skin of patients with atopic dermatitis (AD) is known to have a defective barrier function. The alteration in the skin barrier is shown by the increase in trans-epidermal water loss (TEWL), in other words a poorer barrier to water transport (Seidenari and Giusti, 1995). On the other hand, the data on the permeability of uninvolved AD skin is contradictory. Some authors have reported higher TEWL in patients with AD history (Agner, 1990, Berardesca et al, 1990, Di Nardo et al, 1998, Seidenari and Giusti, 1995, Tabata et al, 1998, Watanabe et al, 1991, Werner and Lindberg, 1985), while others found no difference in comparison to normal skin (Basketter et al, 1998, Di Nardo et al, 1998, Nicander and Ollmar, 2004, Seidenari, 1994, Tanaka et al, 1997). From the results of several studies showing higher susceptibility to irritation in AD patients (Goffin and Pierard, 1996, Nicander and Ollmar, 2004, Seidenari, 1994, Tabata et al, 1998) it was suggested that this might be partly explained by higher skin permeability (de Jongh et al, in press). Impaired skin barrier in AD has often been linked to the different lipid composition and structure of atopic stratum corneum (SC). In this respect, reduced ceramide content and decreased percentages of Cer 1 and Cer 3 have been reported in both involved as well as in uninvolved SC of AD patients (Bleck et al, 1999, Di Nardo et al, 1998, Imokava et al, 1991, Yamamoto et al, 1991). In contrast to this, Matsumoto (Matsumoto et al, 1999) found that the reduction in Cer 1 is restricted to the involved AD skin and does not extend to uninvolved areas: this is consistent with Farwanah's data (Farwanah et al, 2005).

There are rather few data on the permeability of the compromised skin for chemicals. Yosiike (Yosiike et al, 1993) reported increased penetration of theophylline in both involved and uninvolved AD skin. In our parallel study, using the same subjects, the percutaneous penetration of sodium lauryl sulphate increased in uninvolved skin of AD patients (Jakasa et al, in press). Tsai et al. (Tsai et al, 2001a) investigated the effects of chemical and mechanical barrier disruption on skin permeability in an in vitro study using rat skin. They found enhanced skin permeability to both hydrophilic and amphipathic compounds in damaged skin. In other two studies by Tsai (Tsai et al, 2001b and 2003) not only was the penetration of polyethylene glycols (PEGs) of different sizes enhanced but larger molecules were also able to penetrate the skin when the barrier was compromised. Based on clinical experience, Bos and Meinardi proposed the 500 Da rule which states that the absorption of molecules through normal human skin declines rapidly as MW increases over 500 Da (Bos and Meinardi, 2000). On the other hand, topical tacrolimus (822 Da) and pimecrolimus (810 Da) showed to be effective in the treatment of AD (Bos, 2003) suggesting that
larger molecules can penetrate the diseased skin; interestingly, the absorption of tacrolimus declined as the skin healed (Rubins et al, 2005). As regards the role of molecular weight (MW) in penetration through compromised skin in vivo direct, evidence is lacking.

The present study investigated the skin penetration of PEGs of different MWs (150 – 590 Da) into uninvolved skin of AD patients compared to control subjects. PEG is a hydrophilic polymer widely used in corneal and intestinal permeability research. The octanol/water partition coefficient (logK_{ow} ~ -1.6) does not change greatly with molecular size which makes PEGs, suitable model compounds that are not confounded by change in lipophilicity with molecular size (Hollander et al, 1989).

Subjects and methods

Study population

Twenty AD patients, 12 males and 8 females, with a mean age of 29 years (range 18-54 years) and 20 healthy subjects, 11 males and 9 females, with a mean age of 32 years (range 18-55 years), all Caucasians, participated in the study which was carried out in June and July 2004.

The AD patients were recruited from the outpatients clinic of the Academic Medical Center and diagnosed according to the Hanifin & Rajka criteria (Hanifin and Rajka, 1980). We excluded patients who had received systemic therapy, such as corticosteroids and immunosuppressants, or photo-therapy in the past two years. Subjects with concomitant ichthyosis vulgaris were also excluded. The test sites, both mid-volar arms had been free of dermatitis for at least three months prior to the experiment. The total eczema area and severity index (EASI, maximum 72 points) was assessed in the AD patients (Hanifin et al, 2001). The severity of the disease was mild in all the patients and the median EASI was 1.7 (ranging from 0.2 to 22.8). Twelve patients had active AD (pruritic lesions) and eight had inactive AD (they had been free of dermatitis for at least three months, showing only mild signs at the time - scars, scaling, lichenification or dry skin) on body parts other than the test sites.

The control subjects had no visible skin damage and no history of past or present AD or other dermatological diseases.

All the subjects completed the Erlangen questionnaire, from which an atopy score was calculated (maximum 34 points; a score ≥ 10 is considered as atopy) (Diepgen,
AD patients and control subjects had a score of $17.4 \pm 6.6$ and $3.0 \pm 2.4$ (mean ± SD), respectively.

The participants were not allowed to use soap, moisturizers or any other cosmetics or creams on the lower mid-volar arms for 48 hours prior to and during the experiments. Written informed consent was obtained from all the subjects prior to the experiment. The Medical Ethics Committee of the Academic Medical Center, University of Amsterdam, approved the experimental protocol. The study was conducted according to the Declaration of Helsinki Principles.

**Penetration experiment**

An application mixture of PEGs was made by dissolving 47.5 mg of monodispersed PEG150 (MW = 150.17 Da, Sigma, the Netherlands), 50.1 mg of monodispersed PEG282 (MW = 282.34 Da, Acros Organics, NY, USA), 102.9 mg of monodispersed PEG326 (MW = 326.4 Da, PolyPure, Norway), 199.1 mg of monodispersed PEG370 (MW = 370.4 Da, PolyPure, Norway), and 10 g of polydispersed PEG600 (average MW = 600 Da, Sigma, the Netherlands) in 2 ml of water. Subjects were exposed for six hours to the PEG application mixture (180 µL) on the mid-volar arms using patch test chambers (Finn Chambers®, 18 mm in diameter, Epitest Ltd., Finland). These prevented evaporation of water from the test site and this combined with excess PEG insured that the exposure concentration remained constant during the exposure. The TEWL was measured on application sites, before application and after patch removal, using an evaporimeter (VapoMeter SWL2g, Delfin Technologies, Ltd., Kuopio, Finland). Twenty minutes prior the application, the subjects rested with their sleeves rolled up in the examination room, where the temperature was 20-22 °C and the relative humidity ranged between 50 and 60%. Ten minutes after the end of exposure the SC layers were sequentially removed with pre-cut pieces of Diamond tape, 19 x 25 mm (Diamond Ultra Clear tape, The Sellotape® Company, the Netherlands). Templates of Scanpor® tape were fixed to the skin around the application spot to limit the tape stripping to exposed area (18 mm in diameter). The tape pieces consecutively applied to the test site and uniformly pressed with a 1 kg stainless steel roller which was moved 10 times in two directions. The total removal of the SC was evidenced by the shiny appearance of the skin and a TEWL > 100 g m⁻² h⁻¹. Each individual strip was placed into a glass vial and stored at -20 °C until analysis. The SC from a non-exposed site was stripped off and served as negative control.
Analytical procedure
The gas chromatographic method for the determination of PEGs and the spectrophotometrical method for the analysing of proteins in tape strips have been described in detail elsewhere (Jakasa et al., 2004, Jakasa et al., in press).
The concentration of PEGs on each strip was normalized for the amount of proteins and expressed as μg of PEG/μg of protein. Assuming an SC density of 1 g cm$^{-3}$ (Andersen and Cassidy, 1973) and uniform distributions of SC on the tapes and proteins within the SC (μg), the protein mass removed was converted to a volume, enabling the depth of each strip in the SC (x). In our calculation of the SC solute concentration it was assumed that the protein concentration in the SC was 1mg / μL SC.

Data analysis
To estimate the penetration parameters we used an approach based on Fick's second law of diffusion (Crank, 1975) as described by Pirot et al. (Pirot et al., 1997). In this method, two parameters, K and D/L$^2$, are determined by best-fit regression of the concentration pf PEGs as a function of relative SC depth (x/L) to the following equation

$$C(x) = KC_{veh} \left(1 - \frac{x}{L}\right) - \sum_{n=1}^{\infty} \frac{2}{n\pi} KC_{veh} \sin\left(\frac{n\pi x}{L}\right) \exp\left(-\frac{Dn^2\pi^2 t}{L^2}\right)$$  \hspace{1cm} \text{Eq. 1}

where $C_{veh}$ is the applied PEGs concentration (μg cm$^{-3}$), C is the PEG concentration (μg cm$^{-3}$) at depth x (cm), K is the SC/water partition coefficient, L is the total thickness of the SC (cm), D is the effective diffusion coefficient of PEGs through the pseudo-homogeneous SC (cm$^2$ h$^{-1}$) and t is the exposure duration (h). The permeability coefficient ($K_p$, cm h$^{-1}$) for each PEG oligomer was calculated from the relationship $K_p = K^* D/L$. The steady-state flux through the SC should equal the product of $C_{veh}$ and the permeability coefficient ($K_p$, cm h$^{-1}$) and is defined as $K_p = K^* D/L$. The first strip was not included in the regression analysis, as it contained some PEG residues on the surface of the skin after the end of exposure. All concentration data were weighted equally in the regression analysis. Prism 4 (Graph Pad Software Inc., San Diego, CA, USA) and SPSS software were used (SPSS Inc., Chicago, IL, USA) for curve fitting and statistical calculations. Student's t-test and one-way ANOVA with Bonferroni post-test were used for statistical calculations and p value < 0.05 was considered significant.
Chapter 4: Section 4.2

Results

To remove the SC completely, 28 ± 5 strips were needed on average for control subjects and 28 ± 7 for AD patients. The TEWL was higher in the AD patients (8.4 ± 4.3 g m² h⁻¹) than the control subjects (6.3 ± 2.1 g m² h⁻¹, p = 0.015). We found no substantial difference in SC thickness between the two groups (8.7 ± 2.5 μm and 9.4 ± 1.9 μm for control subjects and AD patients, respectively).

Fig 1 shows a typical concentration profile for PEG282 and PEG590 across SC in a control subject and an AD patient together with the fitted curve obtained by non-linear regression analysis (dashed lines). Statistically acceptable curve fitting ($r^2 ≥ 0.95$) was obtained for all the control subjects and AD patients except in the case of PEG150. In four AD patients out of twenty a linear relationship was found between the PEG150 concentration and SC depth, indicating steady-state absorption, to which Fick’s second law cannot be used to derive diffusion coefficient. In two control subjects out of twenty fitting could not be performed for PEG150 because of scattered data points.

**Fig 1:** Concentration decay of PEG282 and PEG590 as a function of normalized position (x/L) in the SC in one control subject and one AD patients after 6 hours exposure to PEG mixture. Non-linear regression analysis was used to fit the equation (Eq. 1) to the experimentally obtained data (dashed lines). The effective diffusion coefficient is calculated from $D/L^2$ value determined from the slope of the curve, while the partition coefficient is determined from $K%C_{veh}$ at the intercept at $x = 0$. 
Chapter 4: Section 4.2

The results are summarized in Table I. The diffusion coefficient decreases with increasing MW of the penetrant. It was approximately twice as high for all PEGs in the AD patients as in the control subjects, except for PEG150, where it was only 60% higher in the AD patients (p < 0.0001 for all PEGs). We also compared the control subjects and the AD patients according to state of disease using one-way ANOVA test. The patients were divided into two subgroups, patients with active and inactive AD. The mean values of diffusion coefficient in three groups were significantly different (p < 0.05 for all PEGs). The mean value of diffusion coefficient in patients with active AD was significantly higher than in the control subjects for all PEG molecules (p < 0.05 for all PEGs). No significant difference was found between patients with inactive AD and the control subjects, or between AD patients with active and inactive AD (Fig 2).

Table I: Penetration parameters of polyethylene glycols (mean ± SD) for AD patients and control subjects.

<table>
<thead>
<tr>
<th>MW Da (kDa)</th>
<th>( D \times 10^{-9} ) (cm² h⁻¹)</th>
<th>( K ) (unitless)</th>
<th>( K_p \times 10^5 ) (cm h⁻¹)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>AD</td>
<td>Ctrl</td>
<td>AD</td>
</tr>
<tr>
<td>150</td>
<td>13.3 ± 6.7</td>
<td>8.4 ± 5.2</td>
<td>1.02 ± 0.29</td>
</tr>
<tr>
<td>282</td>
<td>9.2 ± 5.1</td>
<td>4.5 ± 2.9</td>
<td>0.93 ± 0.38</td>
</tr>
<tr>
<td>326</td>
<td>8.2 ± 4.2</td>
<td>4.5 ± 2.8</td>
<td>0.86 ± 0.35</td>
</tr>
<tr>
<td>370</td>
<td>7.6 ± 3.8</td>
<td>4.1 ± 2.7</td>
<td>0.86 ± 0.37</td>
</tr>
<tr>
<td>414</td>
<td>6.7 ± 3.6</td>
<td>3.5 ± 2.2</td>
<td>0.85 ± 0.37</td>
</tr>
<tr>
<td>458</td>
<td>6.2 ± 3.2</td>
<td>3.2 ± 1.9</td>
<td>0.82 ± 0.38</td>
</tr>
<tr>
<td>502</td>
<td>6.1 ± 3.0</td>
<td>2.9 ± 1.7</td>
<td>0.81 ± 0.38</td>
</tr>
<tr>
<td>546</td>
<td>5.0 ± 3.0</td>
<td>2.4 ± 1.4</td>
<td>0.80 ± 0.43</td>
</tr>
<tr>
<td>590</td>
<td>3.8 ± 2.8</td>
<td>1.9 ± 1.1</td>
<td>0.96 ± 0.53</td>
</tr>
</tbody>
</table>

\( D = \) diffusion coefficient, \( K = \) stratum corneum/water partition coefficient, \( K_p = \) permeability coefficient, AD = AD patients (n=20), Ctrl = control subjects (n=20)
Fig 2: Average diffusion coefficient (D) and partition coefficient (K) of PEGs (150-590 Da) in patients with active and inactive AD after 6 hours dermal exposure. The results are shown as mean ± SD.

The partition coefficient for AD patients was approximately half as large as in the control subjects as for all PEG molecules, except for PEG150, where it was about 60 % of that in the control subjects (p < 0.0001 for all PEGs). We compared all three groups of subjects using ANOVA; again a significant difference was found for all PEGs (p < 0.01 for all PEGs). The partition coefficient was also significantly lower in patients with active and inactive AD than in the control subjects for all PEGs (p < 0.05). There was no significant difference between patients with active and inactive AD, however, the partition coefficient did tend to decrease with state of disease for all PEGs (Fig 2).

Calculated permeability coefficients were nearly the same for both the AD patients and control subjects (Table I).

The inter-individual differences in diffusion coefficient, partition coefficient and permeability coefficient were considerable in both the AD patients and the control subjects. The coefficient of variation in AD patients was 49 % to 73 % for the diffusion coefficient and 29 % to 55 % for the partition coefficient and 32 % to 80 % for permeability coefficient. The coefficient of variation in control subjects was 58 % to 66 % for the diffusion coefficient and 42 % to 58 % for the partition coefficient and 31 % to 56 % for permeability coefficient.
Discussion

The present study assessed the penetration of PEGs ranging in MW from 150 to 590 Da into the SC of AD patients and control subjects. The skin stripping method used enabled us to estimate two penetration parameters, the effective diffusion coefficient in the SC and the partition coefficient between SC and vehicle from which the permeability coefficient could be calculated. According to Fick's law of diffusion, when the SC control mass transfer through the skin, the skin flux of a penetrant is the product of permeability coefficient and the concentration in the SC.

The average diffusion coefficient across SC was about twice as high in AD patients as in the control subjects for all PEG oligomers. The diffusion coefficient also tended to increase with state of disease (Fig 2). These findings are in line with our parallel study using the same subjects, where we found significantly higher diffusion coefficient of sodium lauryl sulphate in uninvolved skin of AD patients (Jakasa et al, in press). The increase in the diffusion coefficient of PEGs was more pronounced in the case of larger PEG oligomers in patients with active AD, which might support suggestion that substantially impaired skin is more prone to high MW compounds entering [Bos, 2003, Rubins et al, 2005]. The higher diffusion of PEG we found in AD skin is consistent with the study by Tsai (Tsai et al, 2001b, 2003), who investigated the penetration of PEGs in vitro in hairless mice. That study assessed the penetration of polydispersed PEG (PEG300, PEG600 and PEG1000) through normal skin and skin damaged by acetone, sodium lauryl sulphate or tape stripping. The penetration of PEGs, expressed as a percentage of the applied dose, increased with the degree of barrier disruption as measured by TEWL in all three disruption models. Shifting of the MW cut-off value for PEG in the damaged skin was also reported. A cut-off value of 414 Da was found in normal skin, but in the skin damaged by acetone, sodium lauryl sulphate or tape stripping, MW cut-off values of 590, 766 and 986 Da respectively were found for the same range of TEWL. However, the amount of larger PEGs that penetrated the skin and reached the receptor fluid was very low and the determined cut-off might reflect the detection limit rather than the real cut-off value [Tsai et al, 2001b, 2003]. This is supported by the finding that the cut-off in that study also shifted to a higher MW after partial tape stripping; this effect was even more pronounced than after skin was damaged by sodium lauryl sulphate or acetone. Tape stripping removes part of the SC which is the rate-limiting barrier for penetration, however, it does not change the composition or structure of the remaining SC, only the thickness of the membrane. A higher penetration can therefore be expected after tape stripping, but the increase will be relatively the same for all MWs.
The diffusion coefficient of a solute decreases as the solute size increases. With respect to diffusion coefficient in the stratum corneum, different authors have proposed different functional forms to describe the effect of solute size (Potts and Guy, 1992, Kasting et al, 1987). In these functions, the diffusion coefficient decreases exponentially with increasing molecular size and predicted a stronger effect of molecular size than observed in this study. Our results showed a gradual decrease of diffusion coefficient of PEGs with increasing MW; in the range of MW from 280 to 590, this relation seemed to be linear (Fig 3).

![Graph showing linear regression analysis for average diffusion coefficients (D) versus corresponding molecular weights of PEG 282-590 Da of AD patients and control subjects after 6 hours dermal exposure to PEG mixture.]

**Fig 3:** A linear regression analysis for the average diffusion coefficients (D) versus corresponding molecular weights of PEG 282-590 Da of AD patients and control subjects after 6 hours dermal exposure to PEG mixture.

This is in good agreement with experimental in vitro data on skin permeability of hydrophilic compounds presented in the paper of Mitragotri (Mitragotri, 2003, Billich et al, 2005). Recent studies revealed that the impact of molecular size on the skin permeability depends on the penetrant hydrophilicity (Mitragotri, 2003). Billich(Billich et al, 2005) showed that in vitro penetration of cyclosporins of MW > 1000 could be substantially increased by introduction of polar side chains. All together, these studies support the existence of different penetration pathways in the stratum corneum, dependently on the physico-chemical properties of the solute. Lipophilic solutes which penetrate predominantly through lipid bilayers exhibit strong size-selectivity: when they approach the MW of the lipid molecules (~ 400 Da),
the diffusion coefficient decreases rapidly. The skin permeation of lipophilic solutes, which represents a large majority of active agents for therapeutic application, would thus be in line with the 500 Da rule. There is increasing evidence however, that the penetration of hydrophilic compounds such as PEGs, occurs via hydrophilic pores in the SC, referred to as porous pathways (Mitragotri, 2003). The existence of such pores in the SC has been hypothesized to be a result of the imperfections in the lipid bilayers. Structure defects are commonly observed in lipid lamellar systems (Cotigan et al, 2000). The permeation rate will depend on the radius of these pores and the radius of the penetrant, while the radius and number of these pores will be determined on the structure and composition of the SC. Higher diffusion coefficient of PEGs in AD skin could be therefore explained by the different lipid composition observed in AD patients in both involved and uninvolved skin (Bleck et al, 1999, Di Nardo et al, 1998, Imokava et al, 1991, Yamamoto et al, 1991), which might result in the presence of more and/or larger pores. Not only the diffusion coefficient but also the partitioning of PEGs into AD skin was different from that in the control skin: the partition coefficient was twice as high in the control subjects as in the AD patients. Although there was no significant difference between patients with active and inactive AD, the tendency for partition to decrease with state of disease was present for all PEG oligomers. Decreased partitioning of PEGs into diseased skin might be explained by the dryness of the AD skin: a smaller amount of water will decrease the partitioning of hydrophilic PEGs into the SC. In contrast to the diffusion coefficient, the partition coefficient was similar for all PEG oligomers. This was consistent with a similar octanol-water partition coefficient over a broad range of MWs (Hollander et al, 1988).

Although the diffusion coefficient was significantly higher in AD patients, the permeability coefficient was nearly the same in both groups due to a compensating decrease in partition coefficient. However, for less hydrophilic compounds, which would more favorably partition into the SC of atopic patients; the influence of diffusion coefficient would result in an increased permeability coefficient. The permeability coefficient, we calculate from the experimentally determined diffusion and a partition coefficient was for the PEGs of MW > 500 Da lower than 5 x 10⁻⁶ cm h⁻¹.

The compounds with such a low permeability will probably have a low relevance for pharmaceutical purposes. However, from a toxicological point of view, one has to keep in mind that also larger molecules are able to penetrate the skin, and as shown in this study this will be even more pronounced when the skin is impaired. Since skin damaged mechanically, chemically or physiologically is not uncommon, when
Chapter 4: Section 4.2

evaluating the health risk associated with skin exposure, penetration of higher MW compounds should be considered.

To summarize, the skin of AD patients showed increased diffusion coefficients for all PEGs when compared to control subjects, and the effect seems to be more pronounced in the case of larger oligomers in patients with active AD. This supports the hypothesis that skin barrier function is altered even in skin that is visibly unaffected and that diffusion coefficient depends on the overall severity of disease. As a consequence, we would expect the defective skin barrier of AD patients to facilitate the absorption of other chemicals, which might result in higher susceptibility and local skin effects.

Acknowledgements
We are grateful to prof. A. L. Bunge and dr. J. Kruse for valuable comments on the manuscript. We are also grateful to N. Mohammadi for the help during development of tape stripping method, and C. E. T. Withagen and F. Calkoen-Kwa for technical assistance. The authors would like to thank the European Community for providing financial support for part of this the study, which was carried out under the Fifth Framework Programme (project acronym: EDETOX).

References:


• De Jongh CM, Jakasa I, Verberk MM, Kezić S: Variation in barrier impairment and inflammation of human skin as determined by sodium lauryl sulphate penetration rate. *Br J Dermatol* advance online publication 27/07/2005


• Jakasa I, de Jongh CM, Verberk MM, Bos JD, Kezic S. Percutaneous penetration of sodium lauryl sulphate is increased in uninvolved skin of atopic dermatitis patients compared to control subjects. *Br J Dermatol* (in press)


• Mitragotri S: Modeling skin permeability to hydrophilic and hydrophobic solutes based on four permeation pathways. *J Contrl Rel* 86: 69-92. 2003
Chapter 4: Section 4.2
