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Transdermal delivery of theophylline from alcohol vehicles

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Abstract

The fluxes of theophylline (Th) through hairless mouse skin from suspensions in straight alkyl chain alcohols have been measured (J_i). The fluxes of theophylline from these first applications was least from methanol (C_1), increased by almost 100-fold for fluxes of theophylline from pentanol (C_5), hexanol (C_6), heptanol (C_7) octanol (C_8) and nonanol (C_9), then decreased 10-fold for the flux of theophylline from undecanol (C_{11}). The second application of a standard solute–solvent, theophylline–propylene glycol (Th–PG), was used to assess damage to the skin caused by the first application. The flux from this subsequent application of Th–PG (J_j) was least after application of Th–C_1, increased almost 60-fold after application of Th–C_5, then remained relatively constant after application of theophylline in the longer chain alcohols. The trend in the fluxes of Th–PG in the second application was the same as the trend in the fluxes of Th–PG subsequent to the application of the neat alcohols previously reported. The ratios J_i/J_j showed that there were no significant increases in fluxes of theophylline from the first application without concomitant increases in fluxes of theophylline from the second application ($J_i/J_j = 1.3–2.2$) except for the application of Th–C_3 where $J_i/J_j = 7.7$. Control experiments showed that the fluxes of the alcohols from the suspensions and the back-diffusion of water into the donor phases in the first application, determined using ^{1}H NMR spectroscopy, were of the same magnitude and gave the same trend as from the application of the neat alcohols previously reported.

Keywords: Alcohols; Back-diffusion; Diffusion cell experiments; Skin damage; Solubility; Theophylline

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1. Introduction

Alcohols have been used as components of topical formulations probably since the first topical formulations were developed. However, only relatively recently have systematic investigations of the effects of the physicochemical properties of these alcohol components on the delivery of polar and nonpolar solutes into and through the skin been undertaken. There are two general types of effects that alcohols and other formulation components can have on the topical delivery of solute. First is the effect of the alcohol on the solubility of the solute in the formulation and hence on the ability of the solute to partition into the skin. Second is the effect of the flux of the alcohol itself into and through the skin which can make the skin more permeable to the solute by damaging the skin in an irreversible manner and/or by changing the ability of the skin to solubilize the solute. The later effect is often referred to as the 'pull' effect while the former is referred to as the 'push' effect (Kadir et al., 1987).

The first systematic investigation of the flux of alcohols into and through skin, which would result in the 'pull' effect, was undertaken by Scheuplein and Blank (1973). Subsequent investigations have been undertaken by Flynn and coworkers (Durrheim et al., 1980, Behl et al., 1980, 1984), Kai et al. (1990) and most recently by Sloan et al. (1997), to name only a few. The majority of the evidence for all the alcohols suggests that flux of the alcohol decreases with increasing alkyl chain length. Scheuplein and Blank (1973) also showed that the effect of the preapplication of neat C_1 and C_2 alcohols on the subsequent flux of C_4 alcohol from water decreased with increasing chain length of the initially applied alcohol. On the other hand, Sloan et al. (1997) showed that the flux (J_j) of theophylline (Th; a polar molecule) from propylene glycol (PG) increased with increasing chain length of the initially applied alcohol and that there was a dramatic increase in J_j after application of the C_4–C_8 alcohols. This difference in results between Scheuplein and Blank and Sloan and coworkers may be due to the differences in polarity between butanol and theophylline. Although they did not evaluate the C_1 alcohol, Kai et al. (1990) observed a trend similar to that observed by Sloan and coworkers for the flux of nicotinamide (also a polar molecule) from water after pretreatment with neat C_2–C_8 alcohols.

However, pretreatment of skin with alcohols is not a convenient method of enhancing topical delivery of a drug. Typically the drug is suspended or dissolved in the formulation, which may act as a permeation enhancer by providing a 'push' to the delivery of the drug. For the nonpolar, lipophilic drug, estradiol, Goldberg-Cettina et al. (1995) showed that its flux through human skin from C_2 alcohol was 2-fold greater than that from water, regardless of the fact that it was 10000-fold more soluble in C_2 alcohol than in water. The flux of estradiol from C_3 alcohol was not different from its flux from C_2 alcohol, and its flux from C_8 alcohol was only 6-fold greater than that from water. Friend et al. (1988) observed a similar trend in fluxes of levonorgestrel through hairless rat skin from C_2–C_8 alcohols. On the other hand, the fluxes of the polar solute, theophylline, from suspensions in the C_1–C_3 alcohols have been reported to follow the opposite trend (Twist and Zatz, 1988a): the flux of theophylline was greatest from C_1 and least from C_3 alcohol. In order to determine that a trend opposite to that observed for the delivery of lipophilic drugs is observed in the delivery of theophylline (a polar molecule) from alcohols, the solubility of theophylline in the C_1–C_{11} straight alkyl chain alcohols and its flux from suspensions (saturated solutions) in the alcohols have been measured under the same conditions that the fluxes of the alcohols were measured (Sloan et al., 1997). Finally, second applications of Th–PG have also been run to determine the effect of the application of theophylline in these alcohols on damage to the skin.

2. Experimental

2.1. Materials

Ultraviolet (UV) spectra were run on a Cary 210 or a Shimadzu UV-265 spectrophotometer.

^{1}H NMR spectra were obtained at 90 HMz on a Varian EM-390 spectrometer. 1-Octanol and propylene glycol were >99% pure, and the 1-hexanol and 1-heptanol were >98% pure from Aldrich. 1-Butanol and 1-pentanol were reagent grade solvents from Mallinckrodt. 1-Propanol was analyzed reagent grade from J.T. Baker. Absolute ethanol was obtained from Aaper Alcohol and Chemical Co. Methanol was certified ACS grade from Fisher Scientific. Analysis of the ^{1}H NMR spectra of the alcohols showed that they did not contain any water. The diffusion cells were glass Franz type from Crown Glass (surface area 4.9 cm^2, 20 ml receptor phase volume). The diffusion cells were maintained at 32°C with a Fisher circulating water-bath (Model 25). The female hairless mice (25–28 g, 12–16 weeks old, SKH-hr-1) were from Charles River. The anhydrous theophylline and deuterated dimethylsulfoxide (DMSO-d_6) in 10 g glass ampules were purchased from Aldrich. The DMSO-d_6 ampules were opened immediately before spectra were run and stored in a vacuum desiccator between spectra.

2.2. Solubilities

The solubility of theophylline in each alcohol ($n = 3$) was determined according to a previously described procedure (Beall et al., 1993). Approximately 100 mg of theophylline was added to each of three test tubes (16 × 100 mm) containing 3 ml of an alcohol. The suspensions were stirred at 23 ± 1°C for 48 h using a star-head stirring bar and magnetic stirrer. The test tubes were insulated from direct contact with the surface of the stirrer. The 48 h was sufficient to ensure the solutions were saturated (Sloan et al., 1986). The suspensions were allowed to settle for 24–48 h, then each suspension was filtered through a 0.45 μm nylon filter using a syringe. Using a calibrated digital pipetter, a 0.5 ml sample of each filtrate was immediately transferred to a 100 ml volumetric and diluted to 100 ml with CH_3OH. The solution was quantitated for theophylline by UV spectroscopy at 270 nm ($\epsilon = 1.03 \times 10^4$ l/mol).

2.3. Diffusion cell experiments

The diffusion cell experiments were run according to previously described procedures (Sloan et al., 1986). Briefly, female hairless mice were sacrificed by cervical dislocation. Their skins were removed by blunt dissection and placed epidermal side up in glass Franz diffusion cells with the dermal side in contact with pH 7.1 phosphate buffer (0.05 M, $I = 0.11$ M, 32°C) containing 0.11% formaldehyde (2.7 ml of 36% aqueous formaldehyde per liter) to prevent microbial growth and to insure the integrity of the mouse skins during the course of the experiment. The theophylline flux from propylene glycol applied 4 h after sacrifice was $6.1 \pm 0.6 \times 10^{-3}$ μmol/cm^2/h, 24 h after sacrifice was $8.3 \pm 1.9 \times 10^{-3}$ μmol/cm^2/h, 48 h after sacrifice was $9.4 \pm 1.2 \times 10^{-3}$ μmol/cm^2/h, and 120 h after sacrifice was $10.0 \pm 1.2 \times 10^{-3}$ μmol/cm^2/h (Sloan et al., 1991). The skins were kept in contact with the buffer for at least 48 h to condition the skins and to allow UV absorbing materials to leach from the skins; the receptor phases were changed at least three times during this time to facilitate the leaching process.

2.3.1. First application

During the first application period of 48 h, 0.5 ml of each suspension of theophylline in alcohol (67 mg/ml for the C_3–C_6 alcohols and 133 mg/ml for the remaining alcohols) prepared in the same way as the solubility sample was applied to the epidermal surfaces of three hairless mouse skins using a calibrated Eppendorf digital pipetter. The donor chamber of each diffusion cell was then sealed with parafilm and kept sealed during each application period except when the receptor phase was sampled and changed. Care was taken to ensure that any condensate on the bottom of the parafilm was returned to the donor phase each time the parafilm was removed. Control experiments showed that parafilm was effective in retaining 97–99% of 1.0 ml samples of C_1–C_4 alcohols in 50 ml beakers ($n = 3$) over a 24 h period and that no water was absorbed (Sloan et al., 1997).

During the course of the first application part of the experiment, 0.3–0.5 ml of suspensions or

saturated solutions were added as needed to the donor phases to maintain the initial suspensions. In this way 0.8–2.0 ml total of the suspensions plus saturated solutions were applied. Receptor phase samples were typically removed at 3, 6, 9, 12, 15, 24, 27, 33, 36 and 48 h, and analyzed for theophylline by UV spectroscopy at 270 nm ($\epsilon = 1.02 \times 10^4$ l/mol). Each time a sample was removed, the entire receptor phase was changed.

After 48 h the donor phases were removed, the donor surfaces were quickly washed with 3×5 ml of methanol to remove all solid theophylline particles and to keep the time of contact between methanol and the skin to a minimum (< 3 min total). The receptor phases were changed and the skins kept in contact with fresh receptor phase for 23 h to allow any residual theophylline and alcohol in the skins to leach out (Siver and Sloan, 1988). Samples of the receptor phases were then taken for analysis for theophylline by UV spectroscopy as above.

2.3.2. Second application

The receptor phases were then changed and a second application of 0.5 ml of a 67 mg/ml suspension of theophylline in propylene glycol was made to all the skins. The donor chamber of each diffusion cell was then sealed with parafilm and kept sealed during the second application period as above except when the receptor phase was sampled and changed. The receptor phases were typically sampled at 1, 2, 3, 4 and 6 h, and analyzed for theophylline by UV spectroscopy as above. Each time a sample was removed, the receptor phase was changed.

2.3.3. Control experiments

Control experiments ($n = 1$) were run to determine if the diffusion of alcohols and propylene glycol and back-diffusion of water in these experiments where suspensions of Th–alcohol or Th–PG were applied were significantly different from those in which only the alcohols were applied (Sloan et al., 1997). These controls were run as had been reported previously but with the following modifications.

During the first application period, 1.0 ml of Th–alcohol (133 mg/ml) or Th–PG suspensions (67 mg/ml) were applied at 0 and 24 h using a calibrated Eppendorf digital pipetter. The weight of the suspension delivered to each skin was determined as the average of repeated ($n = 5$) weighing of 1.0 ml samples of each suspension. The weight of alcohol or propylene glycol in the 1.0 ml aliquot was calculated as the difference in the weight of theophylline in the suspension and the weight of the suspension, assuming a uniform dispersion. The suspensions were kept well stirred, and aliquots for the donor phases and weighings were removed from the middle of the well-stirred suspensions during sampling. During the course of the first application, 0.5 or 1.0 ml of suspensions or saturated solutions was applied as needed to maintain the initial suspensions at 12 and 36 h. In this way, 1.5 or 2.0 ml total of each suspension plus saturated solution was applied over each 24 h period. The donor phase from each diffusion cell was removed at 24 and 48 h using a disposable pipet and bulb suction, weighed and analyzed by ^{1}H NMR spectroscopy as previously described (Sloan et al., 1997).

2.3.4. Flux calculations

The flux (J) of theophylline was determined by plotting the cumulative μmol of theophylline measured in the receptor phase against time and dividing the slopes of the steady-state portions of those plots by the surface area of the diffusion cells (4.9 cm^2). The flux of alcohol or propylene glycol was estimated by dividing the number of μmol of alcohol or propylene glycol lost from the donor phase by time (24 or 6 h, respectively) and surface area of the cell (4.9 cm^2). The back-diffusion flux of water was estimated by dividing the number of μmol of water found in the donor phase by time (24 or 6 h, respectively) and surface area of the cell (4.9 cm^2).

2.4. Solubility parameters

The solubility parameters for the alcohols (δ_v) were calculated using the method of Fedors (1974) as illustrated by Martin et al. (1985a) and Sloan et al. (1986).

2.5. Statistical analysis

Statistical analysis was accomplished using Student's t-test. Unless otherwise indicated, statistical significance is for $p < 0.05$.

3. Results and discussions

3.1. Solubility

The solubility of theophylline in each alcohol is given in Table 1 on a molar and mole fraction scale. Special care was taken to ensure that the alcohols had as little time as possible to evaporate between filtration and sampling of each filtrate for quantitation. This was especially true for the more volatile alcohols where higher solubilities and larger standard deviations (S.D.) were obtained if the time between filtration and sampling was not consistently kept to less than 10 s.

The trend in the solubilities is an odd-higher, even-lower molar solubility pattern up to the C_5 alcohol, with all the solubilities in the 20–30 μmol/cm^3 (mM) range, then a drop in solubility to the 9–11 μmol/cm^3 range for the C_7–C_{11} alcohols. This sort of odd-higher, even-lower trend in solubilities was previously reported for the solubilities of levonorgested in C_1–C_8 straight chain alcohols (Friend et al., 1988). The molar solubility of theophylline in C_1 alcohol at 23°C is essentially identical with that reported by Zhu et al. (1996). On a mole fraction scale (X_i) this translates into a trend of significantly increasing solubility up to the C_5 alcohol, a marked decrease to the C_7 alcohol and then a very gradual increase again to the C_{11} alcohol with all the solubilities in the $1.1–3.4 \times 10^{-3}$ mole fraction solubility range.

Table 1
Solubility parameters for alcohols (δ_x) and solubilities of theophylline in alcohols

Alcohol	δ_x^a (cal/cm^3)$^{1/2}$	Solubility	
		μmol/cm^3 ($\pm$ S.D.)	$X_i^b \times 10^3$
C_1, CH_3OH	13.77	29.5 (0.42)	1.19
C_2, C_2H_5OH	12.58	22.5 (0.74)	1.32
C_3, C_3H_7OH	11.84	30.6 (0.26)	2.27
C_4, C_4H_9OH	11.33	26.8 (0.21)	2.50
C_5, $C_5H_{11}OH$	10.96	31.3 (0.39)	3.40
C_6, $C_6H_{13}OH$	10.68	17.0 (0.15)	2.14
C_7, $C_7H_{15}OH$	10.46	11.3 (0.40)	1.62
C_8, $C_8H_{17}OH$	10.27	10.4 (0.058)	1.67
C_9, $C_9H_{19}OH$	10.13	9.74 (0.075)	1.73
C_{10}, $C_{10}H_{21}OH$	10.00	9.39 (0.67)	1.83
C11, C11H23OH	9.90	9.09 (0.17)	1.92
PG	14.8	53.1 (0.56)	3.88

[a] Calculated according to the method of Fedors (1974).
[b] Mole fraction solubilities.

The molar solubilities previously reported (Twist and Zatz, 1988a) for theophylline in the C_1, C_2 and C_3 alcohols at 37°C (47, 26.7 and 22.8 μmol/cm^3, respectively) and the trend in those solubilities are quite different from the values reported here at 23°C or from the value for theophylline in C_1 reported by Zhu et al. (1996) at 25°C. A possible explanation for the discrepancies is that it is much more difficult to obtain reproducible solubilities at temperatures higher than room temperature. It is difficult to keep all filtering and transferring equipment at a uniformly higher temperature, and the higher temperature merely exacerbates the problem of evaporation of volatile solvents such as the C_1–C_3 alcohols.

The fact that the peak mole fraction solubility of theophylline occurs with the C_5 alcohol [solubility parameter, $\delta_v = 10.96$ (cal/cm^3)$^{1/2}$], suggests that the δ_i of theophylline is approximately 11 (cal/cm^3)$^{1/2}$ compared to the calculated (Sloan et al., 1986) and experimentally determined (Martin et al., 1980) value of approximately 14 (cal/cm^3)$^{1/2}$. This type of experimental result has also been observed for another polar molecule, methyl 4-hydroxybenzoate (Twist and Zatz, 1988b), where its peak mole fraction solubility was in the C_3 alcohol [$\delta_v = 11.84$ (cal/cm^3)$^{1/2}$], while its calculated δ_i was 13.3 (cal/cm^3)$^{1/2}$. In addition, Martin et al. (1985b) have shown that regular solution theory seldom applies to such polar or hydrogen bonded systems so that peak solubilities in such solvents give unreliable estimates of δ_i. For example, calculation of δ_i for benzoic acid from the densities of solutions of benzoic acid in pairs of alcoholic solvents gave $\delta_i = 13.3$ (cal/cm^3)$^{1/2}$ for methanol–ethanol and 11.3 (cal/cm^3)$^{1/2}$ for butanol–octanol (Martin et al., 1985b). Similar results were ob-

Table 2
Fluxes of theophylline from alcohols (J_i), amounts of theophylline leached from skin after theophylline/alcohol removed (C_s), second application fluxes of theophylline from propylene glycol (J_j) and J_i/J_j ratios

Alcohol	J_i ($\pm$S.D.) (μmol/cm^2/h)	C_s ($\pm$S.D.) (μmol)	J_j ($\pm$S.D.) (μmol/cm^2/h)	J_i/J_j
C_1	0.054 (0.011)	0.78 (0.26)	0.041 (0.031)	1.3
C_2	0.12 (0.044)	1.22 (0.11)	0.061 (0.032)	2.0
C_3	0.49 (0.11)	2.89 (0.42)	0.064 (0.011)	7.7
C_4	1.30 (0.28)	15.5 (4.1)	0.67 (0.25)	1.9
C_5	4.62 (0.97)	39.9 (4.2)	2.5 (1.1)	1.8
C_6	4.90 (0.16)	38.1 (9.3)	2.6 (0.97)	1.9
C_7	4.97 (0.53)	12.7 (1.2)	2.9 (0.27)	1.7
C_8	5.00 (0.82)	11.0 (1.8)	3.2 (0.31)	1.6
C_9	6.30 (0.91)	13.1 (1.2)	2.9 (0.92)	2.2
C_{10}	3.00 (0.46)	3.06 (0.43)	1.4 (0.46)	2.1
C_{11}	0.46 (0.044)	5.22 (0.54)	1.3 (0.32)	0.4
PG	0.0096 (0.0012)	0.91 (0.016)	0.015 (0.0032)	0.6
Control [a]			0.013 (0.0022)	

[a] Contact with buffer containing formaldehyde for 96 h, wash twice with 10 ml of methanol, contact with buffer containing formaldehyde for 24 h, then application of Th/PG (Koch and Sloan, 1987).

tained by Zhu et al. (1996) for theophylline in alcohol–water mixtures.

3.2. Diffusion experiments

Suspensions of theophylline in the alcohols were applied to the hairless mouse skins to ensure that the thermodynamic activity of theophylline in each alcohol was the same. However, the application of suspensions made it more difficult to estimate the disposition of the alcohol and water during the single diffusion cell control experiments. It was difficult to completely separate the liquid vehicle part of the donor phase from the theophylline before quantitation by ^{1}H NMR spectroscopy after each 24 h application period. Some vehicle always adhered to the theophylline.

In addition, the apparent crystal form of the suspended theophylline changed during all the experiments to give observable fine needles (Rodriguez-Hornedo and Wu, 1991). These needles were separated, air dried and analyzed by ^{1}H NMR spectroscopy. Their ^{1}H NMR spectra showed the presence of one equivalent of water. This suggests that the formation of the fine needles is due to the formation of theophylline hydrate from the reaction of theophylline with water that had diffused into the donor phase from the receptor phase during the experiments. In contrast to the results previously obtained (Sloan et al., 1997), no separate water phase was observed during any of the experiments where Th–C_4 to Th–C_8 alcohol suspensions were used. This result may be due to the small amount of water that may have back-diffused into the donor phase being tied up as theophylline hydrate.

The flux values of theophylline from the C_1-C_{11} alcohols (J_i) given in Table 2 for the diffusion C_{11} cell experiments increased by almost 100-fold as the alkyl chain length was increased from C_1 to C_5 with a 10-fold increase occurring between the C_3 and C_5 alcohols. There were no significant differences between the fluxes of theophylline from the C_5 to the C_9 alcohols, then flux values decreased by 10-fold as the alkyl chain length was further increased to C_{11}. The increased flux of theophylline from its application in the C_5–C_9 alcohols can be attributed to decreased resistance to permeation of a polar permeate (theophylline) by skin that was being treated at the same time with the longer chain alcohols (see below; Sloan et al., 1997).

There were no significant differences in irreversible damage caused by the application of the pure C_1–C_3 alcohols as determined by the second application studies (J_j; Table 2). The relatively

modest increase in damage (J_j) caused by C_3 compared to the C_1 alcohol (a total of 1.5-fold from C_1 to C_3), as determined by the second application studies, does not explain the 9-fold increase in theophylline flux (J_i) as the alkyl chain was increased from C_1 to C_3 in the first application studies. On the other hand, it is obvious that there is a significant increase in damage to the skins caused by the C_4–C_{11} alcohols. While the J_j values for the C_1–C_3 alcohols are 3–4-fold greater than that for the propylene glycol J_j value, the J_j values for the C_4–C_{11} alcohols are 40–200-fold greater. This is the same trend that was previously observed in the fluxes of theophylline from propylene glycol subsequent to application of C_1–C_8 alcohols alone (Sloan et al., 1997). Thus, the increased flux of theophylline from the C_4–C_{11} alcohols is due to damage to the skins caused by the C_4–C_{11} alcohols. This conclusion is supported by the J_i/J_j values given in Table 2, which show that, except for C_3 and C_{11}, the ratio remains essentially constant for all the alcohols. Only the C_3 alcohol increases the delivery of theophylline to a substantially greater extent than it increases damage to the skins.

Irreversible solvent damage cannot be used to explain the fact that the trend in the fluxes of theophylline from the C_1–C_3 alcohols through fuzzy rat skin reported by Twist and Zatz (1988a) ($J_i = 0.65$, 0.29 and 0.21 μmol/cm^2/h from C_1, C_2 and C_3 alcohols, respectively) is in the opposite direction from that reported here. The damage (J_j) caused by the alcohols is essentially the same. A possible explanation is that back-diffusion of water was observed when the C_1–C_3 alcohols were applied to hairless mouse skins in these and previous experiments (Sloan et al., 1997) but apparently not in the experiments by Twist and Zatz (1988a) using fuzzy rat skin. The back-diffusion is observed as a visibly significant increase in donor volume with time. The back-diffusion is not due to prolonged exposure of the skins to the receptor phase. In previous experiments application of the C_1–C_4 alcohols immediately after the mice were sacrificed and their skins placed in the diffusion cells gave similar values for back-diffusion of water into the donor phase (Sloan et al., 1997). In addition, control studies showed that 0.1% formaldehyde in the receptor phase was effective in preventing deterioration of hairless mouse skin with time upon exposure to the receptor phase for up to 120 h (Sloan et al., 1991), so there should not be any significant change in permeability with time. Regardless, the increase in water content in the donor phase changes the solubility of theophylline in the donor phase (0.03 M in C_1 to 0.095 M at its peak solubility in C_1–H_2O) and its crystal form from anhydrate to monohydrate at activities of water > 0.25 (Zhu et al., 1996). In the present experiments, suspensions of theophylline were maintained by using a sufficiently large excess of theophylline in the C_1–C_3 alcohols to compensate for any changes in solubility. Thus, saturated solutions (suspensions) in the donor phases were visibly maintained during the course of the experiments.

Table 2 also gives values for skin concentration of theophylline that were determined by leaching the skins with receptor phase for approximately 24 h after the initial applications of theophylline in alcohols had been removed. It was assumed that the amount of theophylline that leached from the skin gave an indication of the relative abilities of the alcohols to deliver theophylline into the skin (dermal delivery). The trend in skin concentration was similar to the trend in flux: the concentration of theophylline in the skin increased with the increasing chain length of the alcohol. Thus, there was a good correlation between ability to deliver a solute into the skin with ability to deliver a solute through skin.

Results from single diffusion cell control experiments, which were run to determine the disposition of alcohol and water during the application of theophylline in the alcohols, are given in Table 3. The fluxes of theophylline from the alcohols in the first applications (J_i) and in the second applications (J_j) in the single diffusion cell control experiments were not substantially different from the average for all the diffusion cell experiments. The fluxes of alcohol and back-diffusion of water in Table 3 are qualitatively very similar to the results from the determination of the disposition of alcohol and water after the application of the pure alcohols (Sloan et al., 1997). The flux of alcohol and back-diffusion of water decreased in a

Table 3
Control experiment fluxes of theophylline from the alcohols (J_i), second application fluxes of theophylline from propylene glycol (J_j), fluxes of alcohols (J_{ROH}) and back-diffusion of water (J_{H_2O})

Alcohol	J_i (μmol/cm^2/h)	J_j (μmol/cm^2/h)	J_{ROH} (μmol/cm^2/h)	J_{H_2O} (μmol/cm^2/h)
C_1	0.063	0.019	307	221
C_2	0.18	0.032	144	244
C_3	0.64	0.051	118	175
C_4	1.2	0.50	113	62
C_5	5.5	3.7	65	22
C_6	4.7	3.3	36	9
C_7	4.2	3.0	18	3
C_8	5.2	3.5	–	–
PG	0.012	0.017	19	97

regular manner as the chain length of the alcohol increased. Thus, application of a suspension of theophylline in alcohol does not qualitatively affect the flux of the alcohol or the concomitant back-diffusion of water compared to application of the pure alcohol.

4. Conclusions

Although the solubilities of theophylline in alcohols and the trend in the solubilities here are quite different from those previously reported by Twist and Zatz (1988a), the solubilities reported by Twist and Zatz were determined at 37°C instead of 23°C, the trend in solubilities reported here fits the trend in solubilities of another polar molecule (methyl 4-hydroxybenzoate) in alcohols, and the solubility of theophylline in C_1 determined here agrees with that reported by Grant and coworkers (Zhu et al., 1996). In addition, the trend in solubilities of a polar molecule (theophylline) in alcohols here is essentially identical with that for a much more lipid soluble solute (levonorgestrel) complete with the odd-higher, even-lower solubility pattern.

The trend in the fluxes of theophylline from the alcohols through hairless mouse skin is also similar to that in the fluxes of levonorgestrel from alcohols through rat skin, but is opposite to the trend previously reported by Twist and Zatz (1988a) for theophylline from the C_1–C_3 alcohols. In the latter case no back-diffusion of water was reported, so the difference in the trends between the present results and those by Twist and Zatz could be due to differences in permeability of the two types of skins used (mouse and rat) to water. However, increased water back-diffusion, and hence greater water content in the hairless mouse skin (increased hydration) should lead to higher fluxes of solute through the hairless mouse skin rather than lower fluxes. It is also not likely that the difference in the trend is due to the use of theophylline hydrate ($Th \cdot H_2O$) since fluxes obtained from diffusion cell experiments using $Th \cdot H_2O$ suspensions in C_1–C_9 alcohols gave the same trend in and magnitude of fluxes as reported here (Sloan et al., unpublished results).

Although these results show that the trends in solubilities in alcohols and fluxes from alcohols by theophylline (a polar molecule) fit similar trends reported for lipophilic molecules, it is not clear that other polar molecules will behave in a similar manner.

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