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An *in vitro* study of the effects of formulation variables and product structure on percutaneous absorption of lactic acid

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Synopsis

The efficacy of lactic acid-containing products is linked to their ability to deliver it to specific skin strata. The penetration of L+ lactic acid to different skin layers of porcine skin from various emulsions was measured *in vitro* using flow-through diffusion cells. The effects of pH, propylene glycol, product structure, and mode of application on percutaneous absorption of lactic acid were investigated. The absorption of lactic acid from oil-in-water (o/w) emulsions was measured at pH 3.8 and 7.0. The effect of propylene glycol (5%) as a penetration enhancer for lactic acid was also investigated from an o/w emulsion. The emulsion was applied either as a finite-dose 2-µl topical film or as a 75-µl "infinite"-dose occluded patch on a 0.64-cm^2 skin disc. A key finding was that the effects of changes in product compositions such as vehicle pH and propylene glycol on percutaneous absorption of lactic acid depended on the application mode. Increasing the aqueous phase acidity in an oil-in-water emulsion enhanced lactic acid delivery in the finite dose but not in the infinite-dose application. Finite-dose films were significantly more efficient than infinite dose for lactic acid delivery to tissue compartments. The penetration enhancer propylene glycol was more efficacious at the infinite-dose application. However, it also significantly enhanced lactic acid delivery to viable epidermis in the finite-dose application. Finally, the effect of emulsion phase structure on lactic acid uptake was investigated by comparing delivery from oil-in-water (o/w), water-in-oil (w/o), and water-in-oil-in-water (w/o/w) multiple emulsions with identical compositions. The total tissue delivery of lactic acid from the three emulsions was in the order of o/w > w/o/w > w/o.

INTRODUCTION

Alpha-hydroxy acids (AHA) such as lactic or glycolic acid are weak organic carboxylic acids in which there is a hydroxyl group at the two or alpha (α) position along the carbon chain (1). Many AHAs are found in natural products such as fruits and milk that have long been used as ingredients in cosmetic products. For more than thirty years, certain AHAs have been used in cosmetic products as buffering agents at concentrations of 1–2%. More recently, they have been used in cosmetic formulations at concentrations of 2–15% and as superficial chemical peelers by dermatologists at concentrations of 25–

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70% (2,3). Clinical studies have shown that topical treatment with AHAs, especially lactic and glycolic acids, can moisturize dry skin (4), relieve hyperkeratotic conditions such as moderate xerosis (5), and alleviate signs of photoaging (6). In recent years, this has led to the introduction of large numbers of AHA-containing cosmetic products in the marketplace with great consumer acceptance.

The efficacy of AHA-containing products is linked to their ability to deliver these actives to specific skin strata. Depending on the type and formulation, the AHAs can act either at the stratum corneum or at the deeper, viable tissue level. AHAs enhance the extensibility and the water-binding capability of stratum corneum (7). They may modulate stratum corneum (SC) formation through diminished cellular cohesion between corneocytes at the lowest levels of the SC (4,8). The benefits of smaller water-soluble AHA homologues such as (L+) lactic or glycolic acid is believed to be related to their ability to enhance epidermal cell turnover (9) and collagen and mucopolysaccharide synthesis in the dermis (10).

It is well known that percutaneous absorption depends not only on the nature of the active but also on the vehicle composition. AHAs are currently formulated in a wide variety of cosmetic creams and lotions with differing pH, compositions, or product structure. Although all these products claim efficacy, very little is known about skin absorption of AHAs from complex emulsion systems. Only a few reports (11–13) of systematic study on uptake of AHAs to various skin strata from topical application have been published. Moreover, results of some of these studies appear to be in conflict. For example, in one study (11), decreasing the pH of the aqueous delivery vehicle from 7.4 to 3.8 did not affect skin penetration of glycolic acid (pKa = 3.8), whereas in another (13), changing the pH of an oil-in water emulsion vehicle from 7.0 to 3.0 led to a significantly greater glycolic acid delivery.

The objective of this study was to gain insights into how absorption of small water-soluble AHAs into various skin strata could be modulated by compositional and structural changes in the delivery vehicle. Percutaneous absorption of (L+) lactic acid (pKa = 3.8) through dermatomed porcine skin was measured in an *in vitro* flow-through Bronaugh diffusion cell (14) using well characterized emulsions as test vehicles. The effects of vehicle pH and propylene glycol (as a penetration enhancer) on skin permeation of lactic acid were studied using an oil-in-water (o/w) emulsion. The o/w emulsion was applied either as a 2-μl topical film or as a 75-μl "infinite"-dose (i.e., in large excess) occluded patch on a 0.64-cm^2 skin disc. Comparison of the results provided insights into penetration pathways of lactic acid in stratum corneum.

The effect of vehicle structure on delivery was studied by comparing distributions of lactic acid to different skin strata from topical application of oil-in-water (o/w), water-in-oil (w/o), and multiple (water-in-oil-in water [w/o/w]) emulsions. The composition of the emulsions was kept constant to minimize the effect of formulation variation on AHA delivery. The role of emulsion structure on dermal delivery of a water-soluble active, glucose, in an infinite-dose situation has been studied (15). No similar study for AHAs, either in an infinite-dose or in consumer-relevant finite-dose application, has been reported in the literature.

EXPERIMENTAL

MATERIALS

L+[^{14}C(u)] lactic acid, specific activity 150 mCi/mmol, was obtained from American Radiolabelled Chemicals Inc. The following chemicals were used in formulation of the emulsions: a hydrophilic surfactant (Synperonic PE/F127, a block copolymer of ethylene oxide and propylene oxide; ICI Surfactants, Wilmington, DE); a lipophilic surfactant (Hypermer A60, a modified polyester; ICI Surfactants); lactic acid (USP grade; Purac); paraffin oil (Penreco); and propylene glycol (Fischer Chemical). The scintillation cocktails used were Ecolume™ (ICN), Scintiverse7 Scintanalyzer™ (Fischer Chemicals), and NCS-II-Tissue solubilizer (Amersham Canada Limited).

PREPARATION OF EMULSIONS

All emulsions were prepared from the same formula: paraffin oil 35% w/w, Hypermer A60 2.8% w/w, Synperonic 1.2% w/w, lactic acid 8% w/w, pH adjuster KOH, and balance water. The hydrophilic lipophilic balance (HLB) (16) for Synperonic, was approximately 20, and that of Hypermer was between 2 and 4. The calculated HLB of the surfactant mixture was 9.0. The radiochemical concentration of lactic acid in all the emulsions was 30 μCi/g. The emulsions were stored at 4°C overnight before use in the experiments.

The simple emulsions (o/w or w/o) were prepared by adding the aqueous phase, containing unlabeled lactic acid and the L-[^{14}C(u)] lactic acid, to the oil phase at 65°–70°C. For the o/w emulsion, the hydrophilic surfactant was in the aqueous phase and the lipophilic surfactant was incorporated in the oil phase, whereas for the w/o emulsion both the surfactants were in the oil phase. A coarse emulsion was first formed by mixing the two phases at 65°–70°C in a Tekmar RW 20 DZM mixer for fifteen minutes at 1500 rpm. The emulsion was then homogenized for five minutes with the Silverson L4R homogenizer.

Although the bulk compositions were the same, the interfacial compositions varied depending on the formulation procedure. The adsorption of surfactant monomers at the oil–water interface involves dissociation of the surfactant aggregates in the bulk phase to monomers followed by diffusion of the monomers to the interface. The more soluble the surfactant is in the bulk phase, the faster are the aggregate-monomer breakdown kinetics. When the hydrophilic and hydrophobic surfactants are in the water and oil phases, respectively, the aggregate-monomer breakdown kinetics is high for both of them. As a result, both the hydrophilic and hydrophobic monomers adsorb at the oil–water interface during the emulsification process. The HLB of the surfactant mixture at the interface in that situation is quite similar to the HLB of the total system. For the surfactant system (HLB of 9) chosen in this study, such an interface stabilizes an o/w emulsion. However, when the hydrophilic surfactant is dispersed in the oil phase, the aggregate-monomer dissociation kinetics are slow, and consequently only a small amount of the monomer reaches the oil–water interface during the emulsification process. The interface in this situation predominantly contains the low-HLB hydrophobic surfactant that stabilizes a w/o emulsion.

The w/o/w multiple emulsion was prepared by a two-stage emulsification procedure. In the first step, the w/o primary emulsion was formed at 75°C by adding the aqueous phase, containing unlabeled and labeled lactic acid, to the oil phase containing the hydrophobic surfactant. In the second step, the w/o primary emulsion was dispersed at 50°C in an aqueous solution containing the hydrophilic emulsifier. In this case, two separate oil–water interfaces were created, an inner one with the hydrophobic surfactant and an outer one with the hydrophilic surfactant.

EMULSION CHARACTERIZATION

The emulsions were characterized using the light microscope at a magnification of 100 (Zeiss M 80, Germany). The emulsion drop size was determined by the Malvern Mastersizer using the Mie theory of light scattering. The o/w emulsion was distinguished from the w/o emulsion using the water- and oil-soluble dyes methylene blue and Sudan IV, respectively. The characteristic parameters of the emulsions are shown in Table I. The microscopic aspect of the w/o/w multiple emulsion was characteristic of these systems. The mean diameter of the multiple oil globules observed in the w/o/w emulsions was determined to be 155 μm. The globules of the o/w simple emulsion showed a mean diameter of less than 30 μm, and the w/o globules had a mean diameter of less than 35 μm.

SKIN SAMPLES

The *in vitro* percutaneous absorption measurements were carried out with 3–4-week-old female porcine dorsal skin obtained from Buckshire Corp. (Perkasie, PA) and stored at −75°C. The skin was thawed, and adipose tissue and hair were removed. The shaved skin was then dermatomed to 510-μm thickness using a Padgett Dermatome, and 13-mm discs were cut from the dermatomed skin and mounted on Bronaugh flow-through cells (14). After each skin disc was equilibrated for 30 minutes, transepidermal water loss (TEWL) measurements were carried out using an evaporimeter (Servo-Med AB, Stockholm, Sweden) to check its barrier integrity. Skins with TEWL values greater than 5 gm/cm^2/hour were rejected. TEWL measurements were also carried out to monitor the change in skin hydration after product application.

PERCUTANEOUS ABSORPTION MEASUREMENTS

The experiments were carried out at two dose levels, 2-μl topical film (finite dose) or 75-μl "infinite" dose applied on a 0.64 cm^2 skin disc. The product was spread evenly

Table I
Characteristics of the O/W, W/O, and W/O/W Emulsions

Emulsion	Microscopic aspect	Continuous phase
O/W simple emulsion	Simple globules 25–30 μm	Aqueous
W/O simple emulsion	Simple globules 30–35 μm	Oily
W/O/W multiple emulsion	Multiple globules 150–160 μm	Aqueous

over the entire surface using an applicator. The cells were covered with parafilm in the case of infinite dose to avoid evaporation of the vehicle. Phosphate-buffered saline at pH 7.4 was used as the receptor fluid. The flow rate was controlled at 5 ml/hr. The receptor fluids were sampled every half hour for six hours after dosing the skins. At the end of six hours each flow cell was washed with deionized distilled water three times to remove the excess formulation from the surface. In the case of the infinite-dose application, the excess emulsion was removed with a cotton swab before washing the skin. The skin was dismounted from the cell and carefully swabbed with a Kimwipe™. The stratum corneum was obtained from the skin disc using nine tape strippings (3M Scotch Magic™ Tape). TEWL measurements indicated that the corneum barrier was completely removed by nine tape strippings. The epidermis was then scraped from the dermis using a scalpel, and the dermis was digested in the tissue solubilizer solution. The applicators, cotton swabs, Kimwipes™, cell washes, cell ring washes, wash pipets, tape strips, epidermis, dermis, and the receptor fluids were assayed using a Beckman scintillation counter after addition of 15 ml of scintillation cocktail in each vial.

RESULTS

EFFECT OF pH

The percutaneous absorption of lactic acid (pKa = 3.8) from an oil-in-water (o/w) emulsion was measured at aqueous phase pH values of 7.0 and 3.8. The o/w emulsions were applied either as a 2-μl topical film or as a 75-μl "infinite" occluded dose. Evaporimeter measurements after the application of the topical film on the skin (Figure 1) showed a rapid rise in the water flux followed by a gradual decrease to a steady-state level that was higher than that from an untreated skin. The flux decay curve can be characterized by an initial rapid diffusion, which is characteristic of free water followed by a slow diffusion of water that is bound to either the emulsion film and/or the corneum. The TEWL data suggest that the topical 2-μl o/w film hydrated the skin for about 10–15 minutes. In contrast, in the infinite-dose situation, the skin remained hydrated for the duration of the study due to the large reservoir in the donor side and the occlusion provided by the parafilm.

The amounts of lactic acid in different tissue compartments after six hours (study duration) are shown in Figure 2 for topical film and in Figure 3 for infinite-dose applications. The results are expressed as the percentage of the applied dose as well as the micrograms of lactic acid per square centimeter (based on a measured skin disc size of 0.64 cm^2) of the skin tissue. Pairwise comparisons were carried out using a two-tailed Student's t-test (17) to obtain the significance of difference in the tissue concentrations at the two pH levels.

The effect of pH on the percutaneous absorption of lactic acid depended on the mode of application. When delivered from a topical film, significantly more ($p < 0.01$) lactic acid penetrated the skin at the acidic pH (Figure 2). Decreasing the pH of the 2-μl o/w emulsion film from 7.0 to 3.8 increased the total delivery by four times from 6.5% to more than 25% of the applied dose. The active concentrations in the SC and the epidermis were significantly higher ($p < 0.01$) at the lower pH, and the concentration in the dermis was directionally greater. Similar penetration enhancements at acidic pH

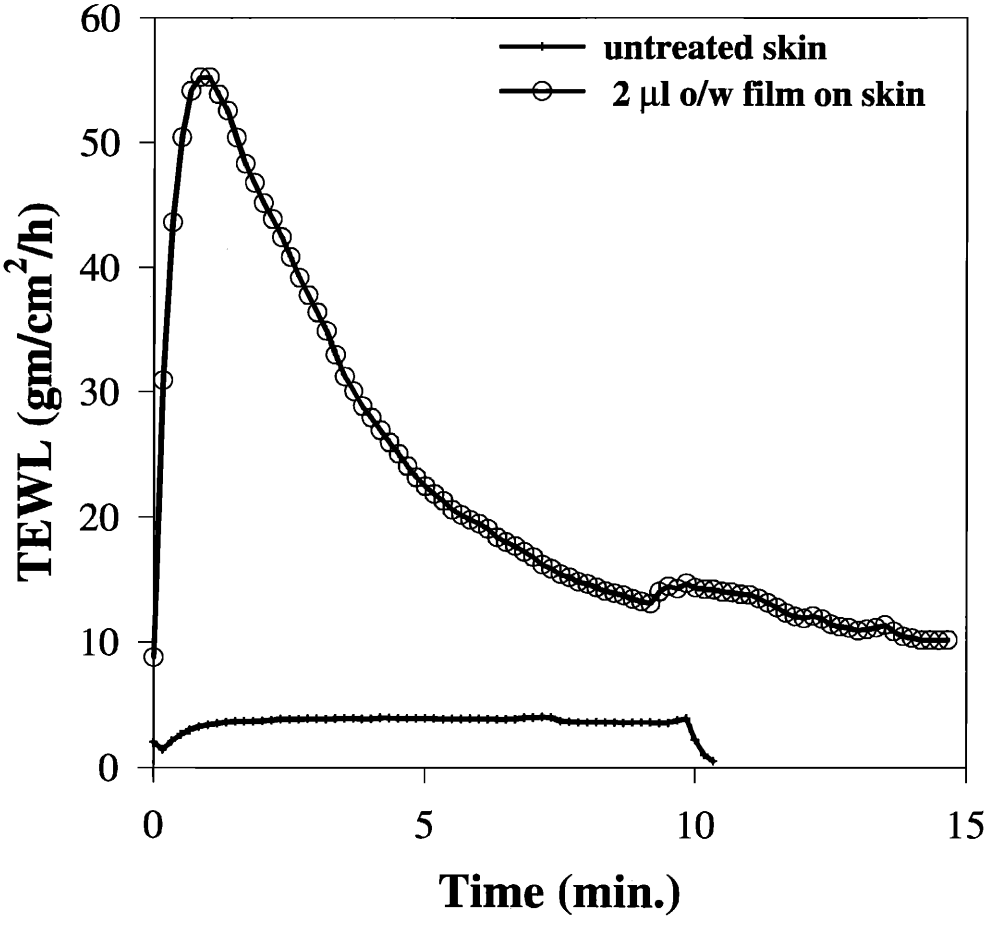

Figure 1. Transepidermal water loss measurements (TEWL) after topical application of a 2-µl oil-in-water emulsion film on the skin surface.

have been reported for lactic and glycolic acid absorption to viable human skin in *in vitro* penetration studies (13). However, the lowering of pH did not have any effect on lactic acid penetration in the infinite-dose situation (Figure 3). In this case, the amount in the SC and epidermis at acidic and neutral pH are quite similar. The difference in the dermal concentrations at the two pH levels was not statistically significant. A similar lack of pH effect in the infinite-dose situation has been observed for the *in vitro* permeation of glycolic (11) and amino (18) acids through mammalian skin.

The receptor phase flux at pH 3.8 and 7.0 for finite-dose application is shown in Figure 4. The effect of pH was compared using a completely nested three-way ANOVA (17) (cells within time points within pH level) statistical design. The analysis was done using the SIGMASTAT (Version 2.0) software (Jandel Scientific Software, San Rafael, CA). The analysis indicated that there was no statistically significant difference ($p = 0.213$). Thus, although there was a directional increase at pH 3.8, the difference in the mean values among the two different levels of pH was great enough to exclude the possibility that the difference was just due to random sampling variability after allowing for the

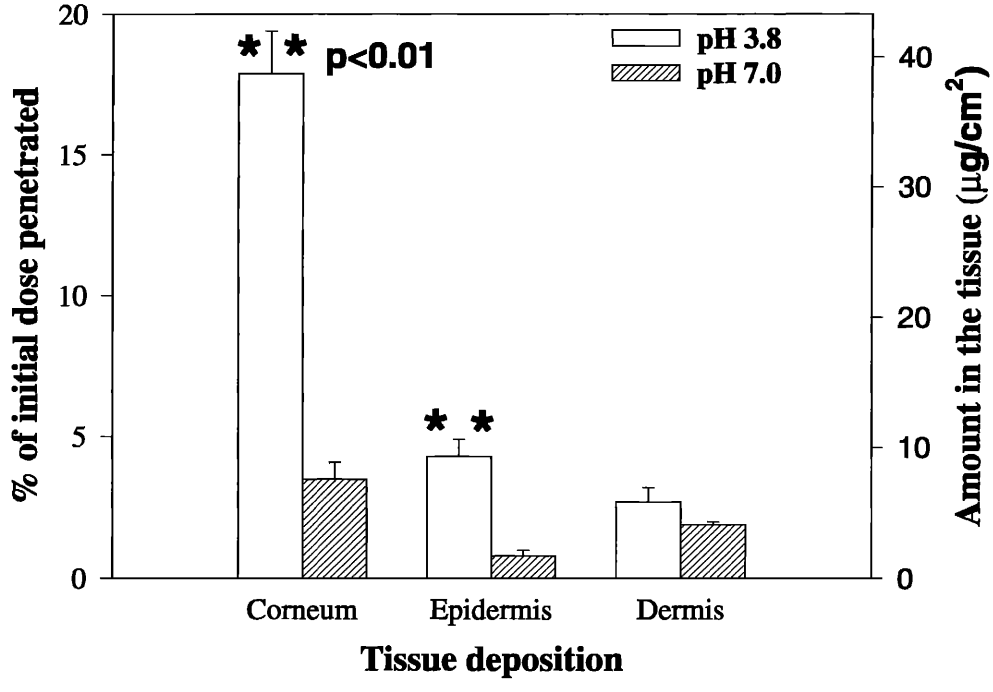

Figure 2. Tissue deposition of lactic acid six hours after application of a 2-µl finite-dose o/w emulsion film at pH 3.8 and pH 7.0 (n = 7). Values are mean (n = 7) ± standard error of mean (SEM). The cumulative receptor penetration at six hours at pH 3.8 is 0.3% ± 0.1 SEM and that at pH 7.0 is 0.2% ± 0.0 SEM.

effects of differences in time points and cells. The cumulative receptor flux profiles as a function of time for the two application modes are compared in Figure 5. In the infinite-dose situation, a steady state was reached within two hours.

The epidermal and dermal concentrations of lactic acid six hours after application of an oil-in-water emulsion are shown in Table II. The tissue concentrations are calculated based on epidermal and dermal thicknesses of 48 and 448 µm, respectively. The data shows that it should be possible to deliver mMolar level of AHA in the living skin tissues from a typical cosmetic rub-on product. Enhanced epidermal cell turnover by lactic and glycolic acid has been suggested (9) as a possible mechanism for their anti-aging efficacy. The results presented here suggest greater bioavailability of α-hydroxy acids in the SC and epidermis at acidic conditions, which may lead to higher efficacy. However, these *in vitro* observations need to be validated with *in vivo* measurements.

A comparison of the finite- and infinite-dose delivery data (Figures 2 and 3) shows that the finite-dose film delivered more lactic acid to the stratum corneum and comparable amounts to the epidermis. The greater efficacy of the finite-dose film is a consequence of a rapid increase in the active concentration in the applied film following application due to evaporation of water. The results highlight the fact that the changes in the thermodynamic activity of the active in a finite-dose film can often be a significant factor in active delivery to skin (19).

EFFECT OF PROPYLENE GLYCOL

The effect of 5% propylene glycol (PG) as a penetration enhancer for lactic acid from

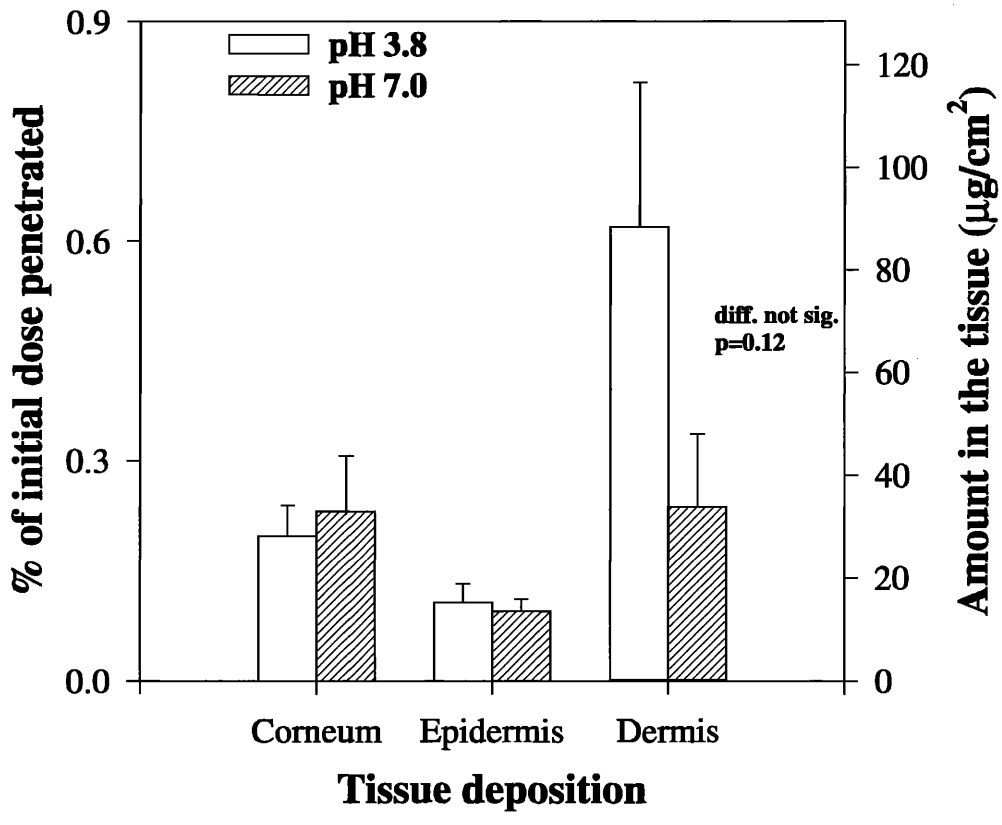

Figure 3. Tissue deposition of lactic acid six hours after application of a 75-µl o/w infinite-dose emulsion at pH 3.8 (n = 6) and pH 7.0 (n = 7). Error bars represent SEM. The cumulative receptor penetration at six hours at pH 3.8 is 0.01% ± 0.01 SEM and that at pH 7.0 is 0.01% ± 0.0 SEM.

oil-in-water emulsions was investigated. The low concentration of propylene glycol used in this study is typical of PG levels in cosmetic products containing α-hydroxy acids. The tissue concentrations for infinite-dose and topical film are shown in Figures 6 and 7, respectively. The time dependency of the transdermal penetration of lactic acid in the infinite-dose situation, assessed by the cumulative absorption in the receptor phase, is shown in Figure 8.

Propylene glycol is more efficacious in the infinite-dose situation. It significantly enhances the active level in the tissue fractions (Figure 6) as well as in the receptor fluid (Figure 8). This is expected, as the penetration enhancement effect is related to the amount of loading of the enhancer. However, significant enhancement of lactic acid delivery to viable epidermis was observed even for consumer-relevant topical-film application (Figure 7). It remains to be seen whether such enhancement could be correlated with the greater anti-aging efficacy of the formulation.

EFFECT OF PRODUCT STRUCTURE

The *in vitro* percutaneous absorption of lactic acid from the o/w, w/o, and w/o/w emulsions was determined using topical application of 2-µl product film. The amounts in

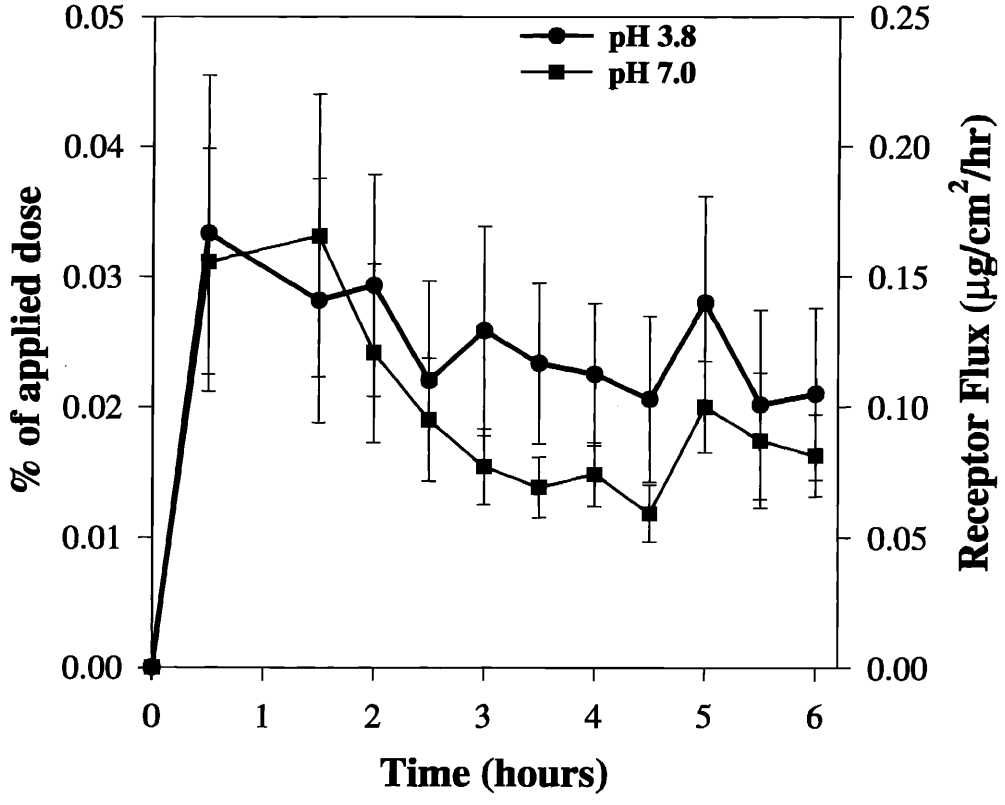

Figure 4. Receptor phase flux profiles of lactic acid delivered from a 2-μl o/w emulsion film at pH 3.8 (n = 6) and pH 7.0 (n = 7). Error bars represent SEM.

different tissue compartments are shown in Figure 9. The total deposition and absorption of lactic acid as a percent of applied dose was in the order of o/w > w/o/w > w/o. Compared to the w/o emulsion, the o/w emulsion delivered significantly more ($p < 0.05$) lactic acid to all the tissue fractions. Compared to the w/o/w emulsion, the o/w emulsion delivered significantly more ($p < 0.02$) to the SC and dermis and directionally more to the viable epidermis. The receptor-phase flux profiles were significantly different with the three different emulsions (Figure 10). With o/w emulsion, receptor flux went through a maximum in about three hours, whereas with the other two emulsions, the flux increased to a plateau after one hour. It should be noted that in most of our studies with o/w emulsion, the maximum in the receptor flux occurs within the first hour. The receptor fluxes for w/o and w/o/w emulsions were nearly identical.

DISCUSSION

Percutaneous absorption of lactic acid to tissue compartments can be enhanced by acidic pH and propylene glycol. However, the effects of these formulation changes depend strongly on the mode of application, i.e., finite or "infinite" dose. The percutaneous absorptions of lactic acid for the two application modes are qualitatively as well as quantitatively different.

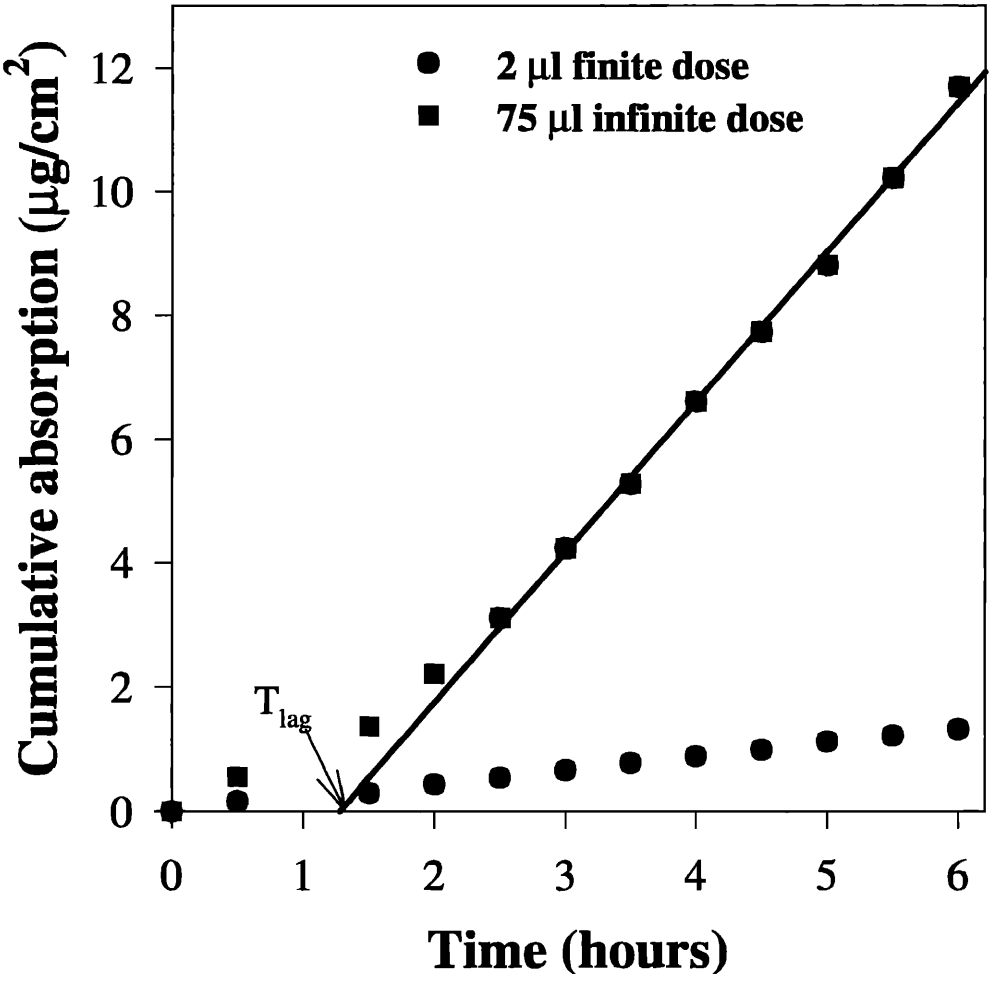

Figure 5. Time dependency of transdermal penetration of lactic acid delivered from a 2-μl finite-dose o/w emulsion film (n = 6) and a 75-μl o/w infinite dose (n = 7) at pH = 3.8 as assessed by the cumulative absorption in the receptor phase. Error bars omitted for clarity.

These penetration results suggest that the penetration pathways for lactic acid in the corneum for the topical-film and infinite-dose applications might be different. In the finite-dose situation, the SC, except for a short (*ca* 20 minutes) period following application, was not hydrated. Thus the active has to penetrate the corneum through a hydrophobic (possibly the lipid) pathway. At pH 3.8, lactic acid is 50% ionized (pK_a = 3.8), whereas at pH 7.0, it is >99.9% ionized. It is known that charged species penetrate poorly through the hydrophobic lipid bilayers. These results are in agreement with *in vitro* measurements by Michaels *et al.* (20), which suggest that the permeabilities of the ionized forms were ~1/20 of those for their un-ionized forms.

Assuming that stratum corneum is the principal barrier to lactic acid penetration, the permeability coefficient, *P,* can be calculated from the receptor flux, *J,* from the following equations (22):

Table II
Effect of pH on the Epidermal and Dermal Concentration of Lactic Acid Six Hours After *In Vitro* Application of an Oil-inWater Emulsion

Mode of application	pH	Epidermis (mM)	Dermis (mM)
2 µl Topical film	3.8	24.9 ± 3.5*	1.6 ± 0.3
	7.0	4.6 ± 1.1	1.1 ± 0.1
75 µl Occluded patch	3.8	23.1 ± 5.6	14.1 ± 4.5
	7.0	20.4 ± 4.5	5.4 ± 2.2

* Standard error of the mean (SEM).

$$J = P\Delta C \tag{1}$$

where

$$P = \frac{KD}{L} \tag{2}$$

In the above equations, ΔC is the difference in the active concentrations between the donor and the receptor sides, K is the distribution coefficient of the active between the top layer of the corneum and the donor phase, and D is the diffusivity of the active in the corneum of thickness L. From Figure 4, the initial receptor flux was 0.16 µg/cm^2/hr,

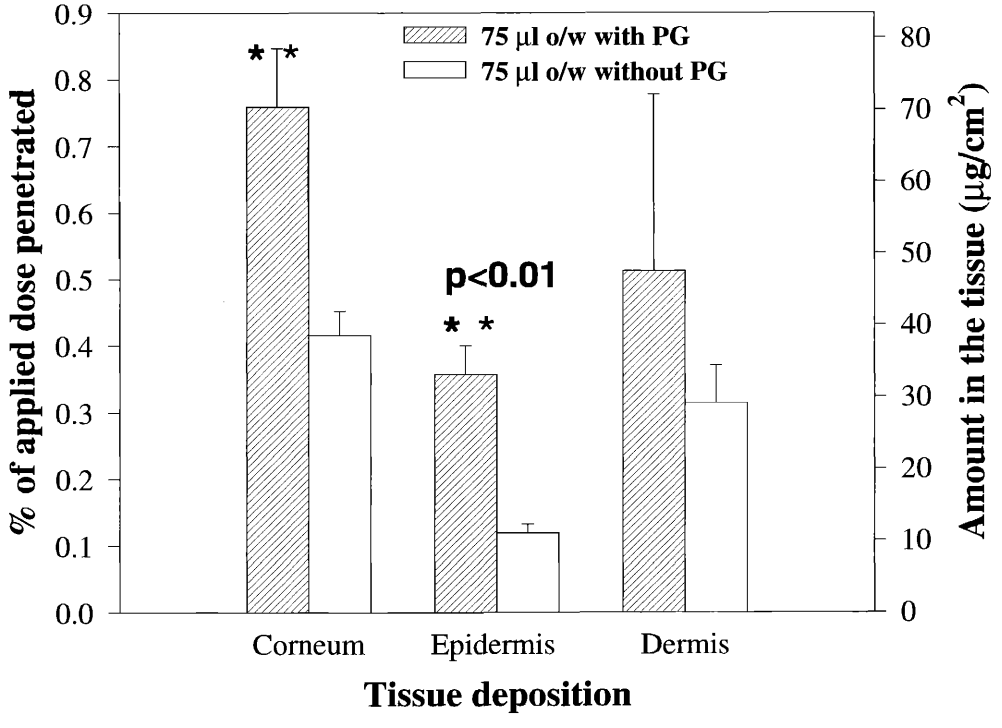

Figure 6. Tissue deposition of lactic acid from a 75-µl infinite dose o/w emulsion at pH 3.8 with (5%) or without propylene glycol. Tissue concentrations (n = 6) were measured six hours after application. Error bars represent SEM. The cumulative receptor penetration at six hours in the presence of propylene glycol is 0.2% ± 0.0 SEM and that in the abscence of propylene glycol is 0.1% ± 0.0 SEM.

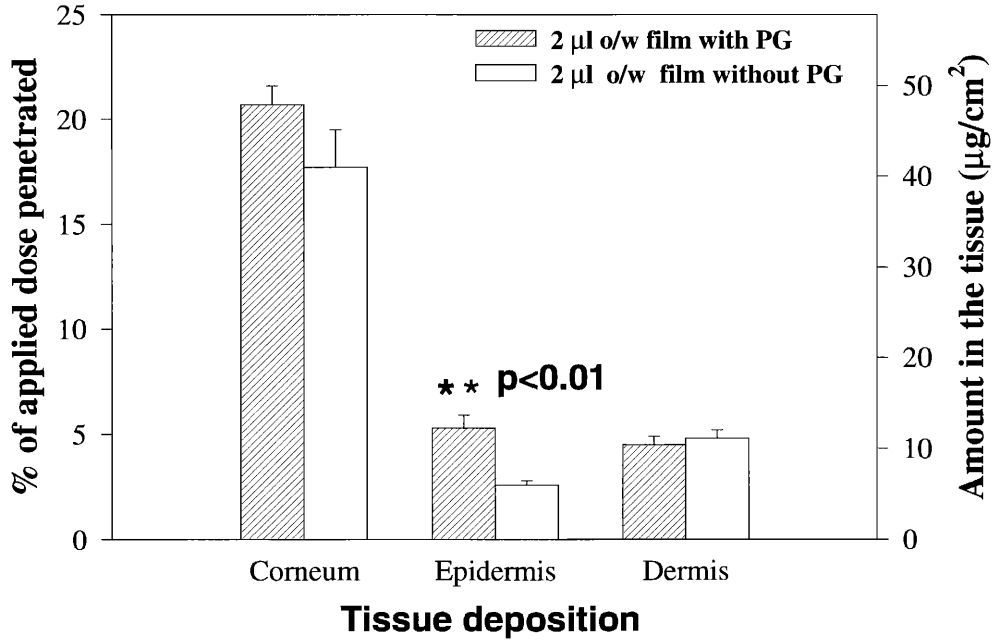

Figure 7. Tissue deposition of lactic acid from a 2-µl finite-dose o/w film at pH 3.8 with (5%) or without propylene glycol. Tissue concentrations (n = 6) were measured six hours after application. Error bars represent SEM. The cumulative receptor penetration at six hours in the presence of propylene glycol is 0.7 ± 0.3 SEM and that in the absence of propylene glycol is 0.05 ± 0.0 SEM.

and the aqueous concentration of lactic acid in the donor side was 0.1778 gm/ml (equivalent to 8% concentration of lactic acid in the total emulsion). The initial permeability coefficient of lactic acid corresponding to these values was calculated as 8.9×10^{-7} cm/hr.

As mentioned earlier, finite-dose receptor fluxes at pH 3.8 and 7.0 (Figure 4) were not significantly different. Receptor fluxes for glycolic acid were found to be pH-sensitive in a 24-hour finite-dose study (13). The lack of pH sensitivity seen in the present study is possibly due to the much shorter (six hours) duration. As the permeability of lactic acid in skin is relatively low, only a very small fraction of the applied dose will reach the systemic circulation in six hours. It is possible that the observed receptor flux in the present study was predominantly due to diffusion through an aqueous shunt or appendagal pathways and hence did not depend significantly on the pH of the vehicle.

The lack of dependance of lactic acid penetration on pH, in the infinite-dose situation, suggests that the skin does not act as a lipophilic barrier in that situation. Here, in contrast to the finite-dose situation, the SC remained hydrated during the course of the study. It has been postulated (18,21) that hydrophilic actives can go through hydrated corneum through aqueous pores or channels and that transport through the water-filled pores is independent of the state of ionization as well as of the oil-water partition coefficient.

The transdermal permeability coefficient for lactic acid was significantly higher in the infinite-dose application. From the steady-state slope of the infinite-dose situation (Figure 5), a flux of 1.21 µg/cm^2/hr was calculated. The corresponding permeability coef-

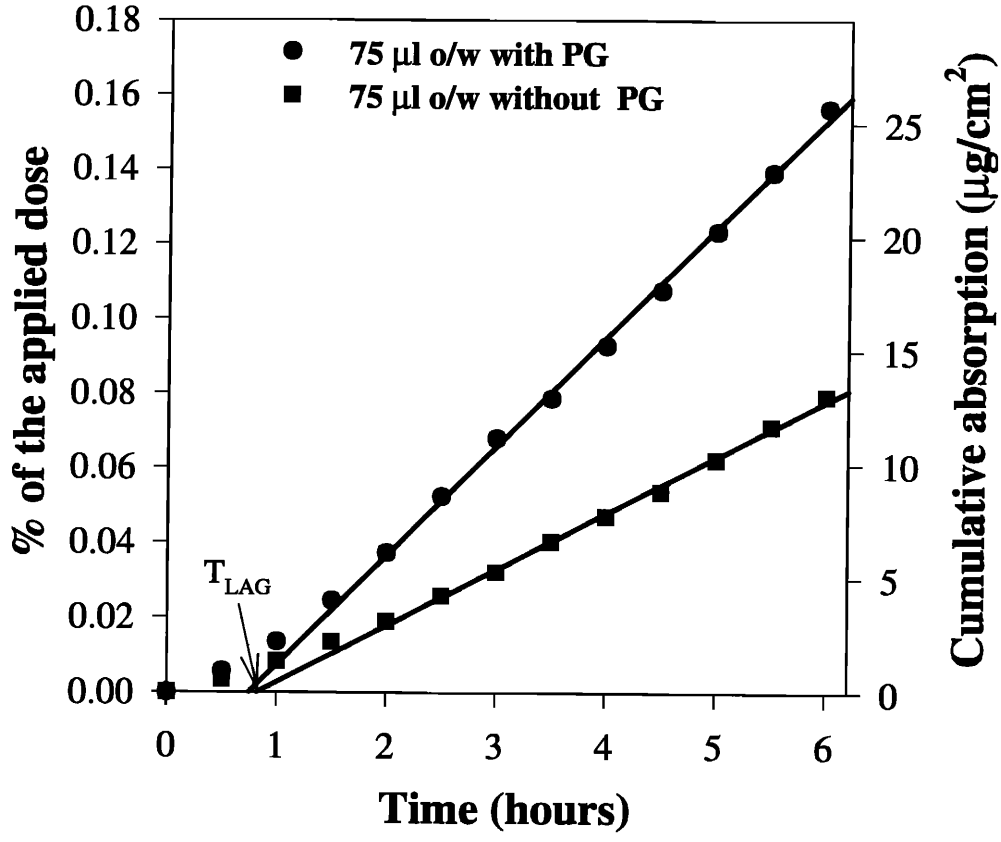

Figure 8. Transdermal penetration of lactic acid delivered from a 75-µl infinite-dose o/w emulsion at pH 3.8 with (n = 6) or without (n = 7) propylene glycol as assessed by the cumulative absorption in the receptor phase. Error bars represent SEM.

ficient was 6.8×10^{-6} cm/hour. This is similar to the permeability of glucose (15) and amino acids (18) in SC.

The diffusivity, D, of lactic acid in the corneum could be calculated using the following equation (22):

$$T_{LAG} = \frac{L^2}{6D} \tag{3}$$

where the lag time, T_{LAG}, is the x-axis intercept of the slope of the flux curve. From Figure 5, the lag time, T_{LAG}, was calculated as 1.276 hours. Assuming a stratum corneum thickness of 15 microns, the diffusion coefficient of lactic acid in corneum was calculated as 8.16×10^{-11} cm^2/sec, which is similar to the diffusivity of nonionic molecules through stratum corneum (22). Such small diffusivity values for transport through aqueous pores might be due to small pore size or constriction in the pores.

Propylene glycol significantly enhanced lactic acid penetration when delivered from an o/w emulsion in the infinite-dose situation. The analysis of the receptor flux data for the

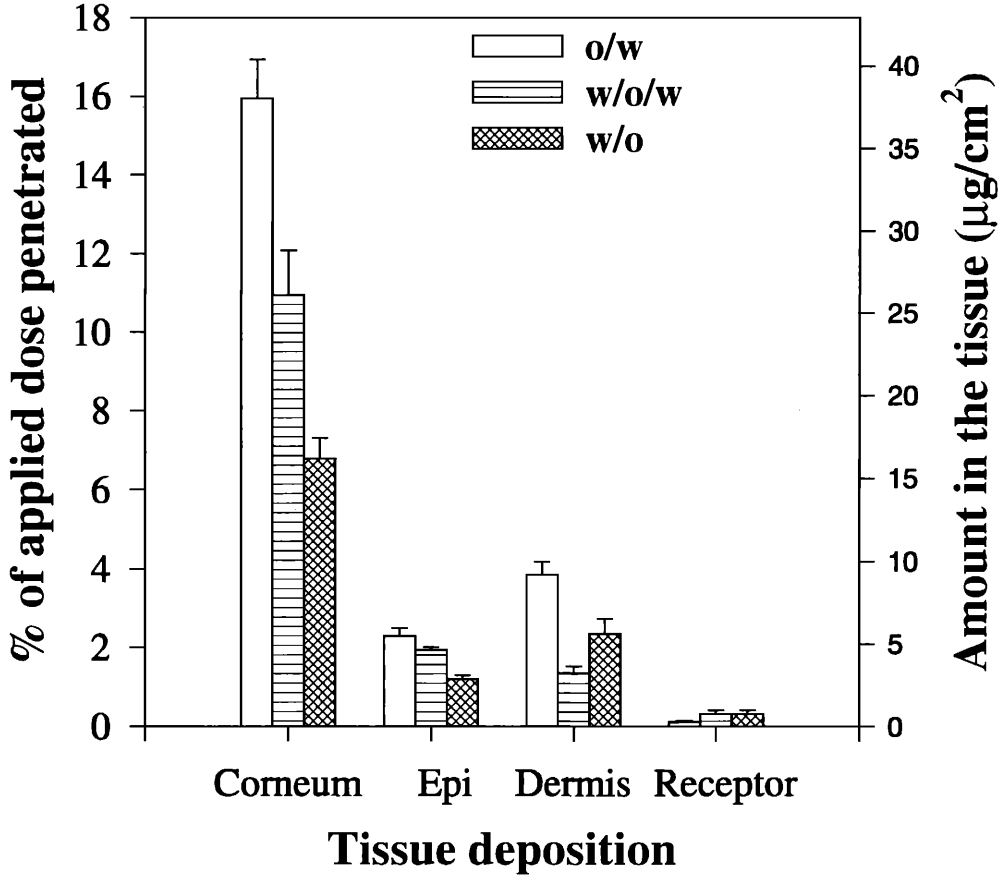

Figure 9. Comparison of deposition of lactic acid six hours after application of a 2-µl finite-dose film of o/w, w/o, and w/o/w multiple emulsions (n = 7) at pH 3.8. Error bars represent SEM.

infinite-dose situation (Figure 8) shows that 5% PG increased lactic acid permeability by about 85%. From the steady-state slopes, the fluxes were calculated as 2.4 and 1.3 µg/cm^2/hr with or without PG. This leads to permeability values of 13.5 × 10^{-6} and 7.3 × 10^{-6} cm/hour with and without PG, respectively. The calculations were done assuming a donor-side lactic acid concentration in the aqueous phase of 0.1778 gm/ml (equivalent to 8% in the emulsion).

Propylene glycol can enhance active penetration in a number of different ways. Depending on the active and the mode of application, PG may enhance penetration by increasing active partitioning into skin and/or by increasing active diffusivity through the SC (23). As discussed earlier, the lack of pH dependance suggests that lactic acid when delivered from an infinite-dose o/w emulsion penetrates the hydrated corneum through water-filled pores. In that case, it is unlikely that active partitioning plays any role in active penetration through corneum. On the other hand, flux data (Figure 8) indicate that PG did not change the lag time (which for a given SC thickness is inversely proportional to the active diffusivity in the corneum) for lactic acid to reach the steady state. However, it is possible (24) that the hygroscopic nature of propylene glycol may

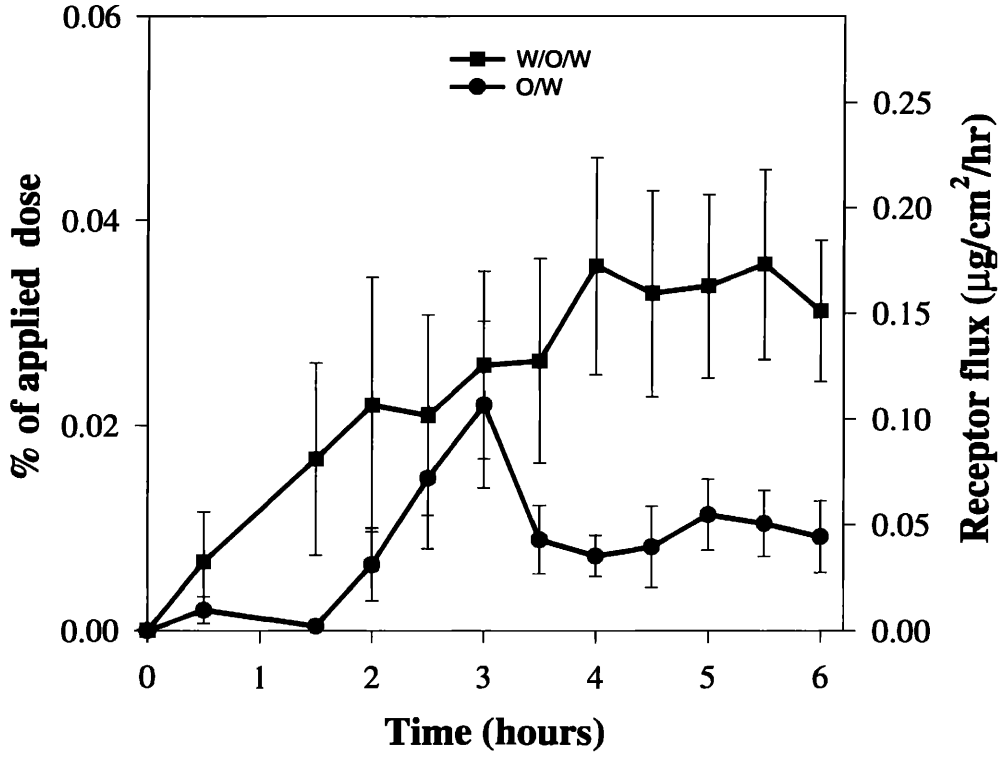

Figure 10. Receptor-phase flux profiles and cumulative absorption (μg/cm^2) of lactic acid delivery from a 2-μl finite-dose film of o/w and w/o/w emulsions (n = 7) at pH 3.8. The receptor flux profile for the w/o emulsion was nearly identical to that of the w/o/w. Error bars represent SEM.

draw water into the stratum corneum, thus increasing its thickness. For a given lag time, a greater corneum thickness would imply a higher diffusivity. However, more research is needed to resolve this issue.

The rate and extent of uptake of lactic acid in various skin strata also depend on product structure. The rank order of the emulsions for tissue delivery of lactic acid from a finite-dose film was o/w > w/o/w > w/o. This is quite similar to that observed for glucose permeation across a silicone membrane and hairless rat skin in an infinite-dose study (15). The greater efficacy of the o/w emulsion for delivering water-soluble actives might be due to a higher concentration of the active in the external phase. Furthermore, it seems likely that with the o/w emulsion, the corneum was hydrated by the external aqueous phase of the emulsion, whereas with the w/o emulsion, the water was confined within the emulsion drops and hence was not immediately available to the SC. In the case of the w/o/w emulsion, in which the external aqueous phase represents only 20% (w/w), the high internal phase volume fraction rendered the emulsion viscous, leading to decreased water mobility.

Although the w/o and w/o/w emulsions delivered less lactic acid to the skin, they might be useful for controlled release of water-soluble actives from topical films (25). The rapid hydration (and consequent water loss from the skin) that occurs when an o/w emulsion

film is applied to skin often lead to a very high peak ("bolus effect") in the active flux. At low pH, this can cause consumer-perceived negatives such as sting. The lower skin hydration with w/o and w/o/w emulsions should lead to a more controlled skin uptake of lactic acid. The plateauing of the receptor flux for w/o/w and w/o emulsions observed in this study (Figure 10) gives some credence to this hypothesis.

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