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Mixture additives inhibit the dermal permeation of the fatty acid, ricinoleic acid

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Abstract

Ricinoleic acid (RA) like many of the ingredients in machine cutting fluids and other industrial formulations are potential dermal irritants, yet very little is known about its permeability in skin. ^{3}H-ricinoleic acid mixtures were formulated with three commonly used cutting fluid additives; namely, triazine (TRI), linear alkylbenzene sulfonate (LAS), and triethanolamine (TEA) and topically applied to inert silastic membranes and porcine skin in vitro as aqueous mineral oil (MO) or polyethylene glycol (PEG) mixtures. These additives significantly decreased ricinoleic acid partitioning from the formulation into the stratum corneum (SC) in PEG-based mixtures. Except for LAS, all other additives produced a more basic formulation (pH = 9.3 − 10.3). In silastic membranes and porcine skin, individual additives or combination of additives significantly reduced ricinoleic permeability. This trend in ricinoleic acid disposition in both membranes suggests that the mixture interaction is more physicochemical in nature and probably not related to the chemical-induced changes in the biological membrane as may be assumed with topical exposures to potentially irritant formulations.

Keywords: Ricinoleic acid; Skin; Permeability; Mixtures

1. Introduction

Fatty acids are often added to topical drugs and cosmetic products to improve skin condition, lubricity, and as a formulation aid in many skin pharmaceutics. Fatty acids such as oleic acid and to a lesser extent its related *cis*-12-monohydroxylated derivative, ricinoleic acid (RA), are known to significantly enhance skin permeation of drugs (Song et al., 2001). However, fatty acids also have industrial uses such as in metal-machining industry where they and/or their derivatives are formulated with cutting fluids to enhance lubricity and thus reduce friction between metal parts (Childers, 1994). It is through such occupational activities that workers' skin can be exposed to various formulations containing fatty acids.

It has often been assumed that these fatty acids and their derivatives are non-toxic to the skin as they are widely used as an emollient in about 19,000 registered cosmetic formulations. However, there have been numerous reports in recent years that the presence of ricinoleic acid in these products can cause

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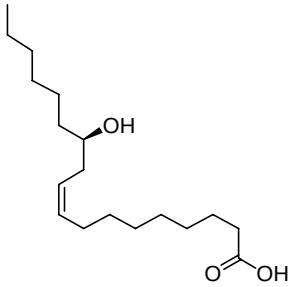


Fig. 1. Chemical structure of ricinoleic acid.

severe dermal reactions (Sai, 1983; Tan et al., 1997). Furthermore, six patients employed in the metalworking industry developed hand dermatitis after exposure to a vegetable-oil-based cutting fluid (Niklasson et al., 1993). After thorough investigation, including patch testing with components in the cutting fluid as well as an oil and cutting fluid series, contact allergy was demonstrated to a fatty acid ester EM-550 in the cutting fluid.

Castor oil, which consists mostly of ricinoleic acid (90%), oleic acid (7%), and linoleic acid (3%), is often included in cutting fluid formulations to enhance lubricity. For this reason, ricinoleic acid (Fig. 1) is the focus of this research. More recent animal studies demonstrated that ricinoleic acid can produce both a pro-inflammatory and anti-inflammatory response in guinea pig skin following topical exposure (Vieira et al., 2001). In spite of these toxicological observations and significant pharmacological data demonstrating that ricinoleic acid alters intestinal motility and increases intestinal mucosal permeability (Gaginella and Philips, 1975), there is little or no information about the dermal absorption and deposition of ricinoleic acid in skin as a single solute or as part of a chemical mixture.

Our working hypothesis is that ricinoleic acid diffusion in skin is modulated by one or more cutting fluid components, and these interactions are not strictly biological in nature (e.g. irritant dermatitis) but physicochemically controlled by one or more chemical components in the mixture. The primary objective of this study was to determine the physicochemical properties of ricinoleic acid in the presence of other cutting fluid formulations. In this regard, mixture pH and ricinoleic acid partitioning from cutting fluid mixtures into the stratum corneum (SC) were empirically measured. The other objective was to determine membrane diffusion of ricinoleic acid in inert silastic membranes as well as porcine skin sections in an in vitro Bronough flow-through diffusion cell system over an 8 h exposure time. Mixture effects observed in silastic membranes as well as the biological membrane may be indicative of predominant chemical interactions modulating solute diffusion in skin. The 8 h exposure is intended to mimic daily occupational exposure and porcine skin was used as the biological membrane because it is anatomically and biochemically similar to human skin.

2. Materials and methods

2.1. Chemicals

Radiolabeled ^{3}H-ricinoleic acid (^{3}H-RA, [12-^{3}H-hydroxy-*cis*-9-octadecenoic acid] with specific activity = 20.00 mCi/mmol) was obtained from American Radiolabeled Chemicals Inc. (St. Louis, MO). Radiochemical purity was 99%. Triazine and linear alkylbenzene sulfonate (LAS) was obtained from Aldrich, Milwaukee, WI, triethanolamine (TEA) and mineral oil (MO), were obtained from Sigma, St. Louis, MO, and polyethylene glycol, average MW 200 (PEG) was obtained from Acros Organics, Morris Plains, NJ. ^{3}H-RA was dissolved in ethanol, and then used to spike castor oil which consisted of predominantly (>90%) unlabeled ricinoleic acid. This radiolabeled fatty acid mixture was used to prepare all surrogate cutting fluid mixtures summarized in Table 1.

Table 1
Ricinoleic acid (RA) mixtures prepared in water and either 5% mineral oil or 5% PEG for physiochemical and diffusion studies

1-Component mixture	2-Component mixtures	3-Component mixtures	4-Component mixtures
RA	RA + TRI	RA + TRI + LAS	RA + TRI + LAS + TEA
	RA + LAS	RA + TRI + TEA	
	RA + TEA	RA + LAS + TEA	

PEG: polyethylene glycol 200; RA: 5% ricinoleic acid, TRI: 2% triazine; TEA: 5% triethanolamine; LAS: 5% linear alkylbenzene sulfate.

2.2. Physicochemical studies

pH determinations: RA solutions were formulated as described in Table 1 and the pH was tested using a Fisher Scientific Accumet AR10 pH meter. Room temperature ranged from 25 to 28 °C and the meter was calibrated to two points.

Stratum corneum (SC)/vehicle partition coefficient determinations: SC/vehicle partition coefficients were determined according to methods previously described in our laboratory (Baynes et al., 2002). In brief, stratum corneum and viable epidermis layers were removed from abdominal skin of a female weanling Yorkshire pig by heat treatment and then treated with 0.25% trypsin (Sigma, St. Louis, MO) to dissolve the epidermis. The remaining SC was dried and weighed (5–8 mg sample) and placed in vials. About 3 ml of the SRA mixtures (Table 1) with ^{3}H-SRA was added to the SC sample vial ($n = 4$), capped, sealed and allowed to remain undisturbed at room temperature for 24 h. At 24 h, 10 μl of the vehicle was removed for direct counts using Ecolume (ICN Costa Mesa, CA). The SC sample was removed, gently blotted to remove excess solution and then analyzed as described below.

2.3. Flow-through diffusion cell experiments

The flow-through diffusion cell system as previously described in the literature (Bronaugh and Stewart, 1985) was used to perfuse porcine skin and silastic (polydimethylsiloxane) membranes. Porcine skin was obtained from the dorsal area of weanling female Yorkshire pigs. The skin was dermatomed to a thickness of 500 μm with a Padgett Dermatome (Padgett Instruments Inc., Kansas City, MO). Silastic membranes (250 μm) were obtained from Dow Corning, Corporation, Midland, MI. Each circular skin and silastic section was punched to provide a dosing surface area of 0.64 cm^2 and then placed into a two-compartment teflon flow-through diffusion cell. Skin and silastic discs were perfused using Krebs–Ringer bicarbonate buffer spiked with dextrose and bovine serum albumin and dosed with 20 μl of 5% RA mixtures described in Table 1. The temperature of the perfusate and flow-through cell was maintained at 37 °C, using a Brinkmann constant-temperature circulator (Brinkmann Inc., Westbury, NY), and the pH was maintained between 7.3 and 7.5. Perfusate flow rate was 4.0 ml/h, and perfusate samples were collected at 0, 10, 20, 30, 45, 60, 75, 90, 105, 120, 150, 180, 240, 300, 360, 420, and 480 min post-dosing. At the end of the perfusion, the dose area was swabbed twice with soapy solution (1% Ivory soap) to determine surface content (Swab 1–2), taped-stripped six times (Tape 1–6) with cellophane tape to determine stratum corneum content, and removed from the skin disc with a 0.64 cm^2 punch biopsy to determine dose area skin deposition. These tissue samples were saved for radiochemical analysis described below.

2.4. Chemical analysis

For determination of ^{3}H-ricinoleic acid, perfusate, swabs, dose skin, and stratum corneum samples were combusted in a Packard Model 306 Tissue Oxidizer (Packard Chemical Co., Downers Grove, IL) and then analyzed by Packard Model 1900TR Liquid Scintillation Counter (Packard Chemical Co., Downers Grove, IL) for total ^{3}H determination.

2.5. Calculations and statistics

Absorption (% dose) in both model systems was defined as the total percentage of initial dose detected in the perfusate for the entire 8 h perfusion period. The apparent permeability (cm/h) of ricinoleic acid in the diffusion cell system was determined from the following equation:

$$\text{Permeability (cm/h)} = \frac{\text{flux } (\mu\text{g}/(\text{cm}^2\,\text{h}))}{\text{dose } (\text{mg}/\text{cm}^3)}$$

Ricinoleic acid flux was determined from the apparent steady state slope derived from a plot of cumulative ricinoleic acid versus time. Tissue disposition parameters such as surface, stratum corneum, and dosed skin were described above. For partition coefficient determinations, radioactivity content in the vehicle mixture and stratum corneum were normalized to 1000 mg vehicle (C_{vehicle}) and 1000 mg SC (C_{sc}), respectively. C_{vehicle} and C_{sc} represents solute concentrations in the vehicle and SC, respectively. The log SC/vehicle partition coefficient (log PC) was determined from the equation:

$$\log PC = \log\left\{\frac{C_{\text{SC}}}{C_{\text{vehicle}}}\right\}$$

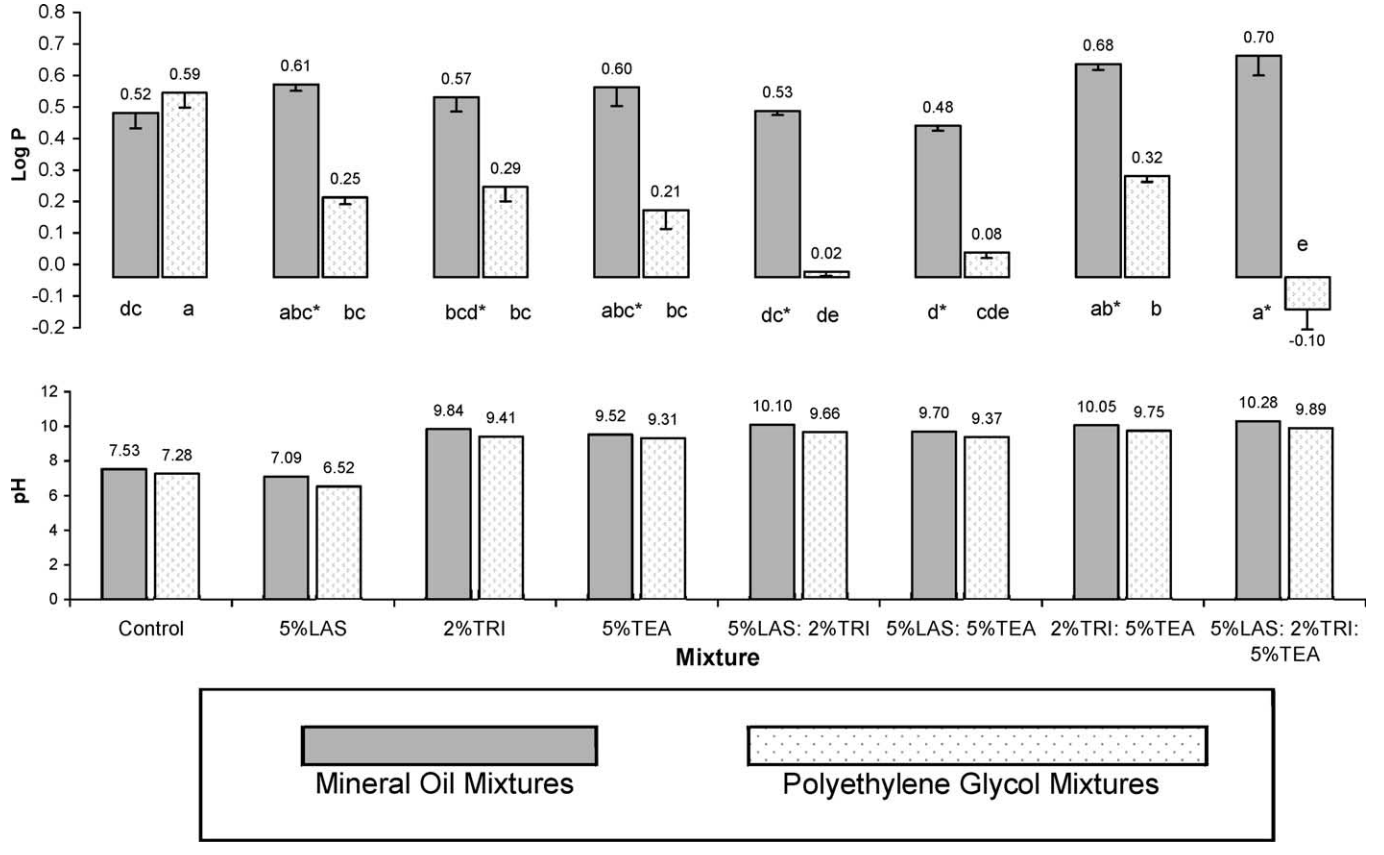


Fig. 2. Influence of cutting fluid additives on the physicochemical characteristics of surrogate mineral oil- and PEG-based cutting fluid formulations. Control refers to ricinoleic acid only and no other additive present in the mixture. Means with different letters represent significant differences between treatments within a mineral oil- or PEG-based mixture ($P < 0.05$). The asterisk (*) indicates significant differences between mineral oil- and PEG-based mixtures for each treatment.

Standard errors were determined for all data sets. For analysis of total absorption, permeability, surface, SC, and dosed area data, multiple comparison tests were performed using ANOVA with significance level at 0.05. All analyses were carried out using SAS 6.12 for Windows software (SAS Institute Inc., Cary, NC). A least significant difference (LSD) procedure was used for multiple comparisons on all parameters assessed.

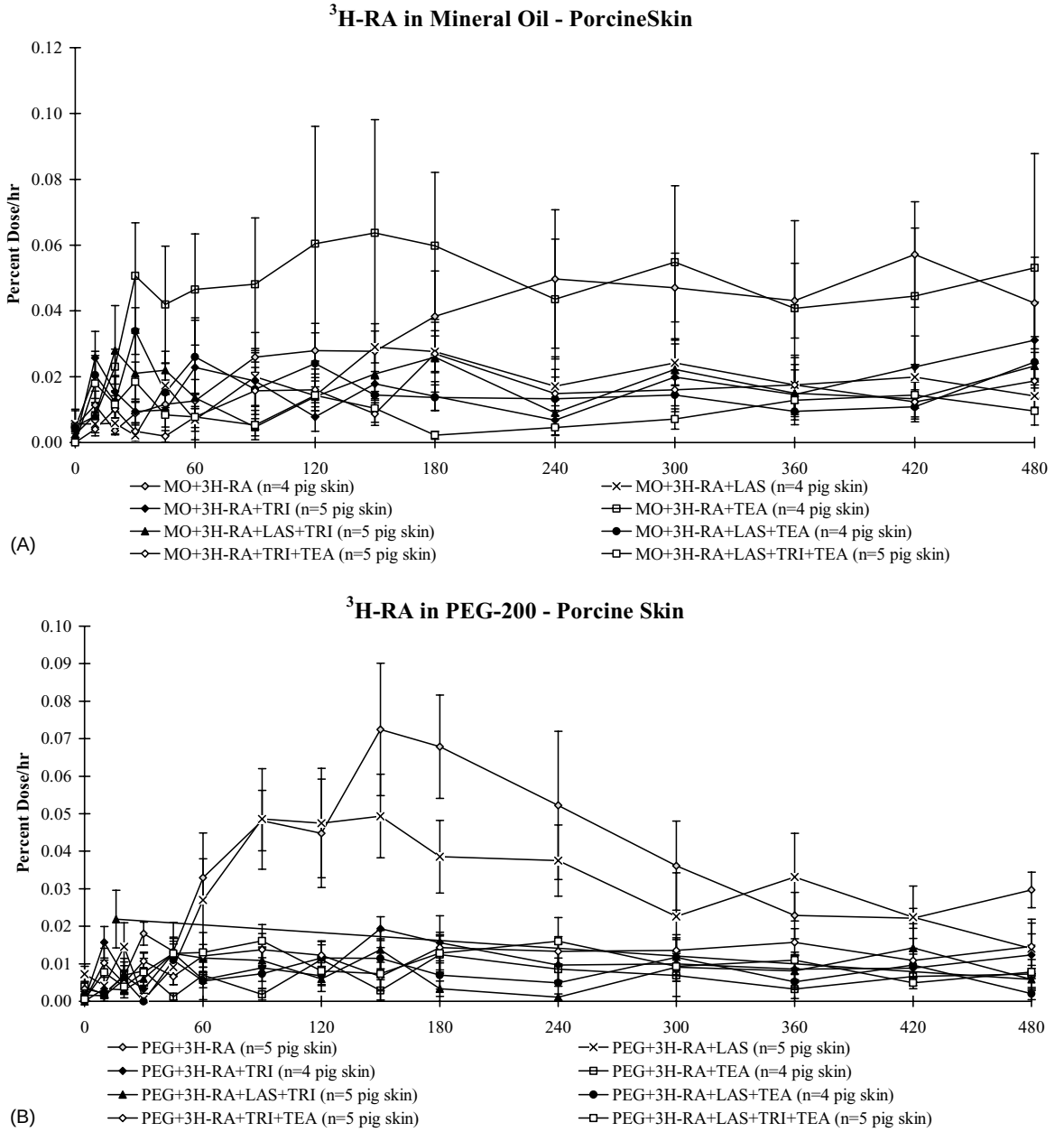
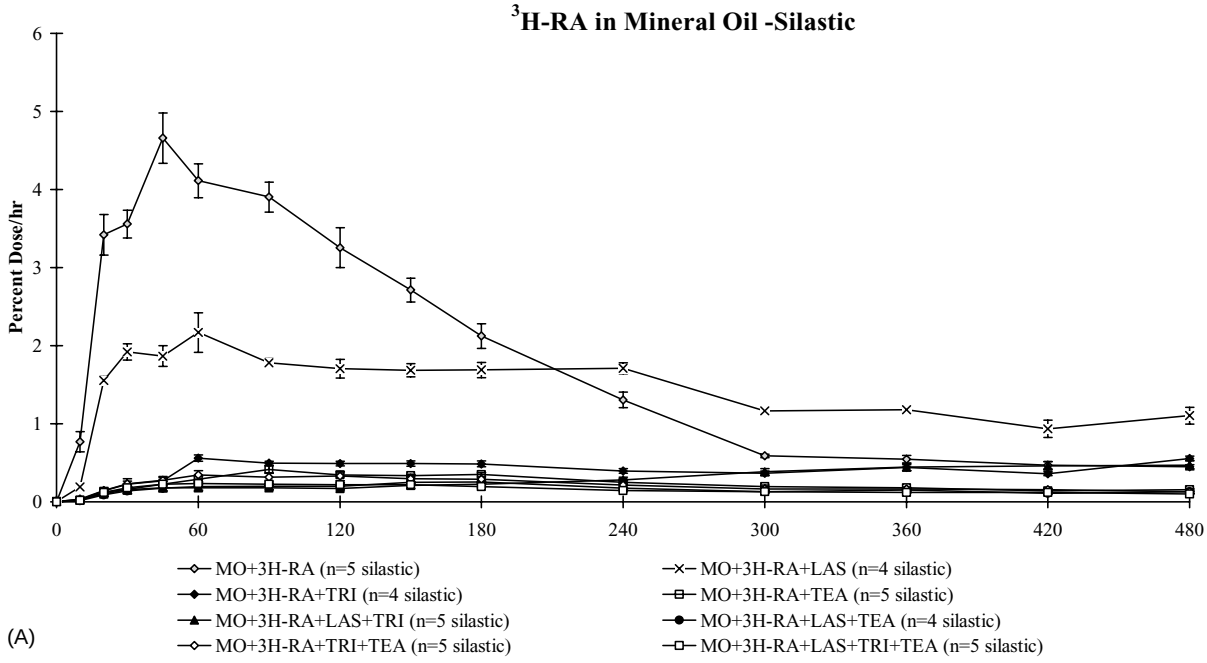
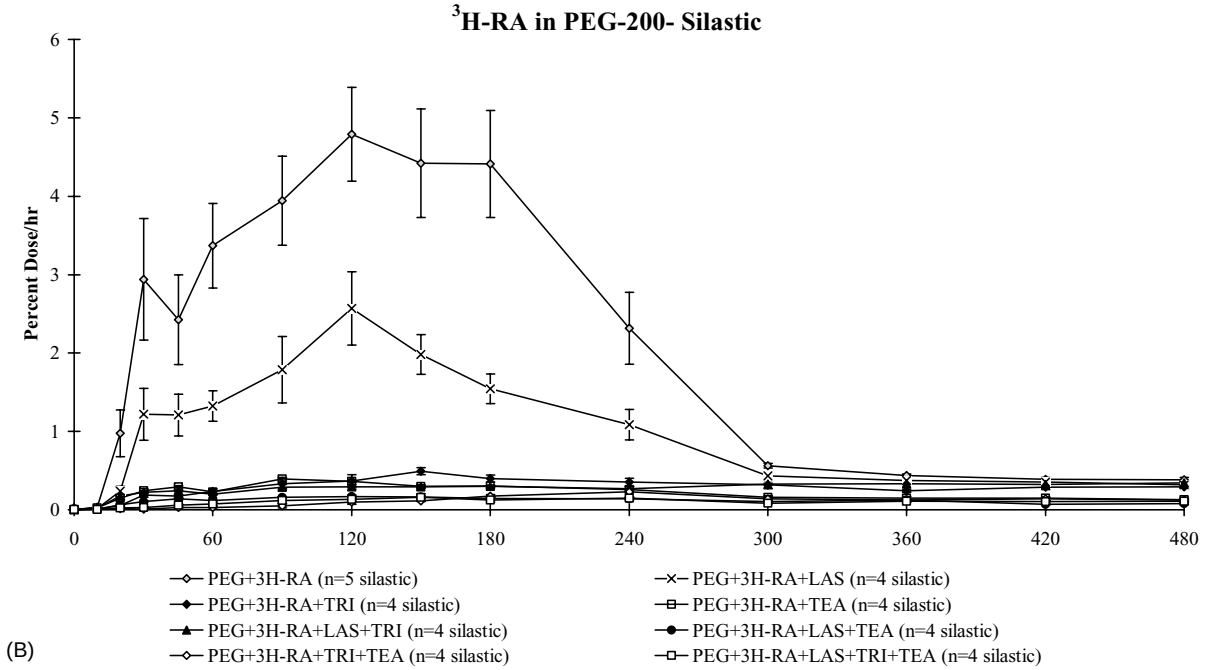


Fig. 3. ^{3}H-Ricinoleic acid absorption flux profiles following topical application of ricinoleic acid mixtures in (A) mineral oil and (B) PEG-200 to silastic membranes in in vitro flow-through diffusion cells system.



(A)



(B)

Fig. 4. ^{3}H-Ricinoleic acid absorption flux profiles following topical application of ricinoleic acid mixtures in (A) mineral oil and (B) PEG-200 to porcine skin membranes in in vitro flow-through diffusion cell system.

3. Results

3.1. Physicochemical studies

The pH of the control mixtures (ricinoleic acid only) or mixtures containing ricinoleic acid and LAS were only within physiological range (6.52–7.53). However, the presence of other additives increased the pH by at least 1–3 pH units to a very basic pH ranging from 9.31 to 10.28 (Fig. 2). Ricinoleic acid partitioning into the stratum corneum was significantly reduced in the more complex PEG mixtures ($P < 0.05$), while this trend was reversed with mineral oil mixtures. In fact, the presence of one or more additives in mineral oil mixtures resulted in significantly greater ricinoleic acid partitioning into the stratum corneum compared with PEG-200 mixtures ($P < 0.05$).

3.2. Dermal permeation and deposition

Ricinoleic acid absorption peaked within 3 h for most mixtures, with the greatest ricinoleic acid peak concentrations being associated with the control mixtures containing PEG in both membranes (Figs. 3 and 4). Eight hours after topical exposure, ricinoleic acid absorption ranged from 1 to 13% dose in silastic membranes, but only 0.1–0.3% dose in porcine skin membranes (Figs. 5 and 6). Compared to other mixtures, ricinoleic acid permeability and absorption in either membrane system was significantly greater when dosed by itself than when other additives were present in the mixture ($P < 0.05$). That is, the presence of cutting fluid additives in these mixtures had a negative effect on ricinoleic acid absorption and permeability. The only exception was in porcine skin exposed to mineral oil mixtures, where TEA significantly enhanced absorption compared to control mixture. It should also be noted that LAS alone had one level of effect, while other additives or combination of additives had a more significant effect on reducing ricinoleic acid absorption and permeability ($P < 0.05$).

At the end of the 8 h perfusion experiments, as much as 5% dose of ricinoleic acid was detected in the dosed skin and as much as 16% dose was detected in the stratum corneum with mineral oil formulations. Considerably, less ricinoleic acid remained in these skin tissues with PEG mixtures and this was statistically significant for 5/8 of the mixtures ($P < 0.05$). Significantly, greater levels of ricinoleic acid were detected in the dosed skin and stratum corneum with the control mixtures (ricinoleic acid only) or with LAS mixtures ($P < 0.05$), and reflected the same general trend observed with the absorption data. That is, the presence of more additives in these mixtures reduced ricinoleic acid deposition in skin tissues. It should also be noted that ricinoleic acid deposition in these tissues was always greater in mineral oil than PEG mixtures, and statistically significant for 6/8 of these mixtures ($P < 0.05$).

4. Discussion

Fatty acids are generally thought to be innocuous, and for this reason included in cosmetics or topical pharmaceutical formulations to enhance dermal absorption of drugs. This absorption enhancement by fatty acids has been attributed to disordering of the highly packed intercellular lipids and other morphological changes (Touitou et al., 2002). Ironically, it is these biological changes that are sometimes associated with fatty acid-induced irritancy in human skin (Stillman et al., 1975). Ricinoleic acid is used to enhance lubricity of metal-machining operations, but in spite of its known dermal irritant effects in workers, its dermal disposition has not been well characterized.

Logically, the degree of irritation associated with related fatty acids is governed by its physicochemical properties (e.g. molecular weight) and its ability to penetrate the skin (Leung and Paustenbach, 1990). Our study demonstrated that although dermal absorption of ricinoleic acid into the perfusate can be minimal (<0.4%), as much as 16% of the dose can be retained in the stratum corneum for 8 h. From an occupational health perspective, this may be significant enough to cause dermal irritation in metal-machining workers.

The most surprising observation from this study was that the presence of cutting fluid additives significantly reduced dermal absorption and skin tissue deposition of ricinoleic acid. These cutting fluid additives are themselves dermal irritants and should theoretically enhance solute permeability as recently demonstrated with related chemical mixtures (Baynes et al., 2003). However, because the opposite effect was observed, this suggests that chemical–chemical

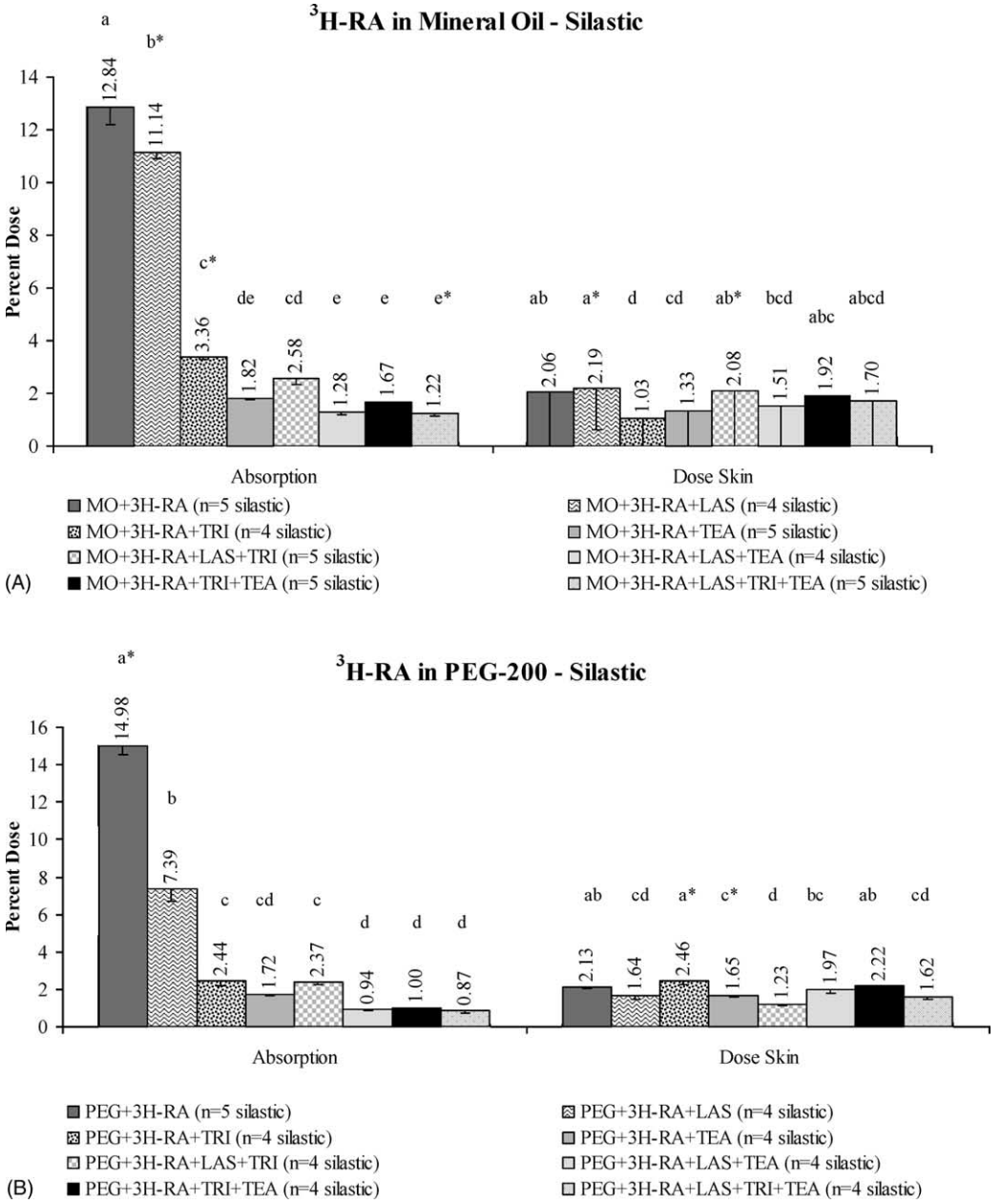


Fig. 5. ^{3}H-Ricinoleic absorption and membrane deposition (% dose) in (A) mineral oil-based and (B) PEG-based mixtures in silastic membrane. Control refers to ricinoleic acid only and no other additive present in the mixture. Means with the same letters represent no significant differences between treatments within a mineral oil- or PEG-based mixture ($P > 0.05$). The asterisk (*) indicates significant differences between mineral oil- and PEG-based mixtures for each treatment.

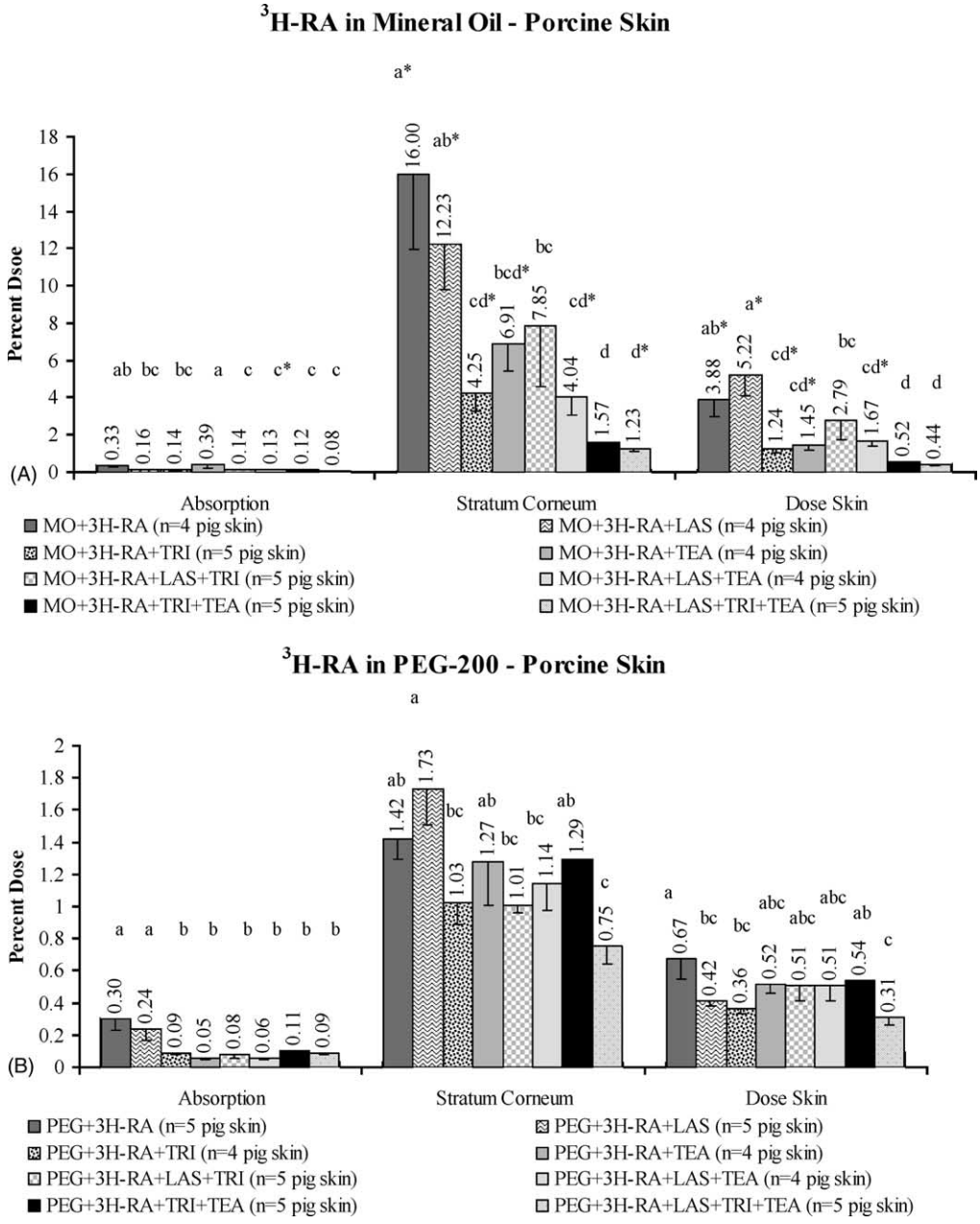


Fig. 6. ^{3}H-Ricinoleic absorption and skin membrane deposition (% dose) in (A) mineral oil-based and (B) PEG-based mixtures in porcine skin sections. Control refers to ricinoleic acid only and no other additive present in the mixture. Means with the same letters represent no significant differences between treatments within a mineral oil- or PEG-based mixture ($P > 0.05$). * indicates significant differences between mineral oil- and PEG-based mixtures for each treatment.

interactions more so than chemical–biological interactions occurred when skin was exposed to these cutting fluid mixtures.

Cutting fluid additives clearly had a significant effect on mixture pH and ricinoleic acid partitioning into the stratum corneum, which further demonstrates that several physicochemical mechanisms modulating ricinoleic acid diffusion in skin were operational. Firstly, ricinoleic acid is a weak acid ($pK_a = 6$), and because the presence of the additives increased the mixture pH by as much as three pH units, it is plausible to assume that this will probably result in the formation of more of the anionic than the free fatty acid form. Although, this study did not characterize the predominant form of ricinoleic acid in these mixtures, accepted partitioning theory suggests that the anionic form or charged state will limit partitioning and membrane diffusion. The free fatty acid form is more likely to exist in the control mixture that has a pH in the range of 7.28–7.53, and will more readily partition into the stratum corneum.

Numerous other studies have demonstrated the effect of formulation pH on dermal absorption, and have inferred from further delipidization experiments that the free fatty acids diffuse through the lipid domain of the stratum corneum and the anionic form diffuses through the protein domain (Swarbrick et al., 1984; Oakley and Swarbrick, 1987; Smith and Anderson, 1995). Even when the skin is subjected to very significant pH ranges, these effects are not observed with lipophilic chemicals (Sznitowska et al., 2001) but only ionizable chemicals. As the stratum corneum is remarkably resilient to highly acidic or alkaline mixtures (pH = 1–12) (Sznitowska et al., 2003), modulations in solute partitioning and diffusion across membranes is not related to pH-induced modifications of the stratum corneum. In the absence of topically applied chemicals, there exist an inherent pH gradient across the skin, i.e. skin surface pH being 5–6 and viable pH being 7.4 (Bouwstra et al., 2003). It is possible that the degree of ionization of ricinoleic acid will increase as it penetrates deeper into the skin (Lieckfeldt et al., 1995) making it more difficult for these weak acids to diffuse across the skin membrane.

The stratum corneum partitioning experiments further demonstrated that ricinoleic acid partitioning in the stratum corneum was significantly inhibited by the presence of cutting fluid additives with PEG-200 but not mineral oil mixtures. This trend may be related to the fact that cutting fluid additives enhanced ricinoleic acid solubility in PEG-200 and thereby reduced partitioning from the dosing mixture into the membrane. At the end of the 8 h exposure in the diffusion cells, this trend was also observed in the stratum corneum and dosed skin layers. These differences between mineral oil and PEG were however not reflected in ricinoleic permeability and absorption in silastic or skin membranes.

One or more cutting fluid additives significantly decreased ricinoleic acid absorption and permeability in both skin and silastic membrane. This interaction was more significant in silastic membrane than skin because of potential interactions between the diffusing fatty acid and other fatty acids in skin. Fatty acids are an integral component of the intercellular lipid domain in skin which is composed of approximately equimolar concentrations of free fatty acids, cholesterol, and ceramides (Bouwstra et al., 2003). It is possible, that interactions between these epidermal fatty acids and ricinoleic acid impeded ricinoleic acid diffusion as it moved into the deeper layers of the viable epidermis. This region of the epidermis contains a greater proportion of free fatty acids while silastic membranes contain no free fatty acids.

Although LAS significantly reduced ricinoleic acid absorption, the other additives triethanolamine and triazine either individually or as a mixture with LAS had a more significant effect on ricinoleic acid absorption. The fact that this was observed in both membranes reinforces the argument that these two additives had a significant effect on mixture pH and possibly the proportion of free acid form available for dermal transport. As an anionic surfactant, LAS is expected to enhance dermal absorption of most hydrophilic solutes (Wilhelm et al., 1991; Xia and Onyuksel, 2000). However, in this case it may have negatively altered fatty acid diffusion by direct chemical complexation with LAS micelles as previously reported with other solute–surfactant mixtures (Chidambaram and Burgess, 2000) or possibly altered lipid pathway in the epidermis. The latter mechanism is not likely, as this surfactant–membrane interaction does not occur in silastic membranes, and yet we observed similar LAS effects on ricinoleic acid absorption in these inert membranes (Table 2).

In summary, the physicochemical observations are consistent with diffusion characteristics of ricinoleic

Table 2
Mean (SEM) apparent permeability of ^{3}H-ricinoleic acid mixtures

Mixture	*n*	Mineral oil permeability[a] (cm/h × 10^{-3})	*n*	PEG–200 permeability (cm/h × 10^{-3})
Silastic membrane				
^{3}H-RA	5	0.668 (0.039) a	5	0.789 (0.062) a
^{3}H-RA + LAS	4	0.276 (0.006) b*	4	0.346 (0.057) b
^{3}H-RA + TRI	4	0.076 (0.002) c	4	0.061 (0.009) c
^{3}H-RA + TEA	5	0.059 (0.003) c	4	0.061 (0.003) c
^{3}H-RA + LAS+TRI	5	0.066 (0.007) c	4	0.047 (0.002) c
^{3}H-RA + LAS+TEA	4	0.034 (0.003) c	4	0.022 (0.003) c
^{3}H-RA + TRI+TEA	5	0.042 (0.007) c*	4	0.012 (0.021) c
^{3}H-RA + LAS + TRI + TEA	5	0.037 (0.001) c*	4	0.014 (0.004) c
Pig skin				
^{3}H-RA	4	0.0032 (0.0005) b	5	0.0065 (0.0014) a
^{3}H-RA + LAS	4	0.0026 (0.0002) b	5	0.0062 (0.0021) ab
^{3}H-RA + TRI	4	0.0024 (0.0006) a	4	0.0022 (0.0003) c
^{3}H-RA + TEA	4	0.0077 (0.0026) b	4	0.0017 (0.0001) c
^{3}H-RA + LAS + TRI	4	0.0043 (0.0011) b	5	0.0017 (0.0004) c
^{3}H-RA + LAS + TEA	4	0.0049 (0.0049) ab*	4	0.0018 (0.0006) c
^{3}H-RA + TRI + TEA	5	0.0026 (0.0026) b	5	0.0022 (0.0004) c
^{3}H-RA + LAS + TRI + TEA	5	0.0028 (0.0004) b	5	0.0034 (0.0003) bc

[a] Means with the same letters represent no significant differences between treatments within a mineral oil- or PEG-based mixture ($P > 0.05$).

* Indicates significant differences between mineral oil- and PEG-based mixtures for each treatment. PEG: polyethylene glycol 200; RA: 5% sulfated ricinoleic acid, TRI: 2% triazine; TEA: 5% triethanolamine; LAS: 5% linear alkylbenzene sulfate.

acid in these complex mixtures. It can therefore be assumed that physicochemical interactions which influenced ricinoleic acid partitioning into the stratum corneum, modulated ricinoleic acid diffusion as evidenced by reduced permeability as the mixture became more complex. Although in vitro diffusion may differ from in vivo diffusion in human skin, physicochemical interactions between ricinoleic acid and cutting additives appear to play a significant role in membrane diffusion. The human health implications here are that the more complex the mixture, the less able ricinoleic acid is to partition and diffuse across skin. This can result in greater retention of these potentially irritant fatty acids in the upper epidermis, which will eventually penetrate into the viable epidermis and absorbed into the blood stream.

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