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Targeted delivery of salicylic acid from acne treatment products into and through skin: Role of solution and ingredient properties and relationships to irritation

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Synopsis

Salicylic acid (SA) is a beta hydroxy acid and has multifunctional uses in the treatment of various diseases in skin such as acne, psoriasis, and photoaging. One problem often cited as associated with salicylic acid is that it can be quite irritating at pH 3–4, where it exhibits the highest activity in the treatment of skin diseases. We have identified strategies to control the irritation potential of salicylic acid formulations and have focused on hydroalcoholic solutions used in acne wipes. One strategy is to control the penetration of SA into the skin. Penetration of the drug into various layers of skin, i.e., epidermis, dermis, and receptor fluid, was measured using a modified Franz *in vitro* diffusion method after various exposure times up to 24 hours. A polyurethane polymer (polyolprepolymer-15) was found to be an effective agent in controlling delivery of SA. In a dose-dependent fashion it targeted delivery of more SA to the epidermis as compared to penetration through the skin into the receptor fluid. It also reduced the rapid rate of permeation of a large dose of SA through the skin in the first few hours of exposure. A second strategy that proved successful was incorporation of known mild nonionic surfactants like isoceteth-20. These surfactants cleanse the skin, yet due to their inherent mildness (because of their reduced critical micelle concentration and monomer concentration), keep the barrier intact. Also, they reduce the rate of salicylic acid penetration, presumably through micellar entrapment (either in solution or on the skin surface after the alcohol evaporates). Cumulative irritation studies showed that targeting delivery of SA to the epidermis and reducing the rapid early rate of penetration of large amounts of drug through the skin resulted in a reduced irritation potential. *In vivo* irritation studies also showed that the surfactant system is the most important factor controlling irritancy. SA delivery is secondary, as formulations with less SA content reduced the rate of delivery to the receptor and yet were some of the most irritating formulations tested, presumably due to the action of the specific anionic surfactant on the barrier. Alcohol content also did not appreciably affect irritation and SA delivery; formulations with considerably lower alcohol content but containing anionic versus nonionic surfactant systems exhibited considerably higher irritancy. Thus the surfactant type was again the predominant factor in those studies, although arguably alcohol plays some role (solubilization of SA). Results showed that both polymers and mild surfactants work in concert to provide the optimal formulation benefits of targeted delivery and reduced irritation. Synergistic relationships among hydroalcoholic formulation components will be discussed along with the mechanisms likely involved in controlling delivery of SA to skin.

INTRODUCTION

Various strategies are being used to control delivery of active substances to the skin. The use of polymers to control the delivery of actives from semisolid preparations has

numerous advantages. Acrylic, cellulosic, block copolymers and, more recently, polyesters are among the polymers that received most of the attention from investigators (1–5). In semisolid preparations, these polymers usually increase the viscosity of the system (2,6) without effect on the rate of delivery of actives (7). Other polymeric systems studied used polymer microparticles that contained the drug and were capable of releasing it over an extended period of time. Won (8) introduced porous solid microspheres into which the drug could be incorporated. Mathiowitz *et al.* (9) presented nonbioerodable and erodable microspheres that were capable of reducing the release rate of actives. Additional patents reference incorporation of cationic polymers (acrylates) and skin-depositing polyurethanes. These polymers are reported to deposit the active drug salicylic acid onto the skin surface or to target penetration into the epidermis from cleansers and emulsions (10,11).

The use of the polyurethane polymer polyethylene glycol-8/SMDI copolymer (polyolprepolymer-15) in controlling the delivery of salicylic acid and lactic acid from topical preparations was recently studied by Fares and Zatz (12). The effect of this polyurethane polymer, polyolprepolymer-15, on permeation was measured *in vitro* using flow-through diffusion cells and dermatomed pig skin. Skin uptake was also evaluated over time using tape-stripping and tissue analysis. The polymer decreased the flux of salicylic acid through pig skin but did not affect the delivery of lactic acid. The polymer increased the overall deposition of salicylic acid in the stratum corneum but did not change the levels of salicylic acid in the viable skin significantly. Skin uptake of lactic acid was not affected by the presence of the polymer. Based on dialysis and cloud point measurements, it was found that polyolprepolymer-15 reduced the activity of salicylic acid in the vehicle via binding, leading to a decrease in permeation. The binding mechanism accounts for the effect of polyolprepolymer-15 on the solutes investigated; salicylic acid was found to bind to the polymer but lactic acid did not. Because of binding, the thermodynamic activity of salicylic acid is reduced in the presence of the polymer and the stratum corneum/vehicle partition coefficient is reduced. As a consequence, the transfer rate into stratum corneum is lower than for a control system without polymer, which also results in a lower rate of passage through the skin.

Another strategy frequently used to control delivery of active compounds to skin is entrapment in surfactant micelles. For topical treatment products this strategy can become problematic since surfactants are used for cleansing but are generally too irritating to be in contact with skin for an extended period of time. Several patents have recently been issued that show the use of surfactant complexes to control delivery of actives (13,14) while maintaining the gentleness of formulations. This technology refers to the formulation of surfactant complexes that produce milder formulations and enhance deposition of salicylic acid onto the skin surface layers. In the first technology (13), an anionic–amine oxide complex was carefully preformed to end up with a charge density of zero, meaning complexation is complete. Thus the system no longer is comprised of anionics or zwitterionics; rather, the complex is "pseudononionic." The irritation potential of the pseudononionic will likely be as mild as typical nonionics. The critical micelle concentration would be very low, thus producing a large micelle reservoir to trap the drug. The irritating anionic moiety is tied up in the complex. A similar technology strategy incorporates complexes of anionics with traditional cationic surfactants (14). The result is also a pseudononionic complex with similar consequences, providing complexation is complete.

Polyolprepolymer-15®, is a hydroxyl-terminated block copolymer of 1,1″-methylene-bis-[4,isocyanatocyclohexane] and 8 moles of ethylene oxide, which makes the polymer soluble in water. The average molecular weight of the polymer is 1,800. This paper reports on the effect of this polymer on the delivery of salicylic acid into skin from hydroalcoholic solutions typically used in acne treatment formulations. It also studies the effect of other components of the formulation, namely surfactants and salts, on salicylic acid delivery and the interactions between these components to control drug delivery and formulation mildness. The relationship of controlled drug delivery to the irritancy of these hydroalcoholic solutions will be investigated. Studies in this report were thus done to extend our understanding of the relationship of the controlled delivery phenomena of the polyurethane polymer and surfactant type and solution behavior to the irritation potential of salicylic acid hydroalcoholic solutions.

MATERIALS

Materials include salicylic acid (SA), phosphate-buffered saline (called PBS, Sigma, St. Louis, MO), scintillation fluid, glacial acetic acid (Fisher Scientific, Fair Lawn, NJ), polyethylene glycol-8/SMDI copolymer (polyolprepolymer-15, Bertek, Inc., Foster City, CA), isoceteth-20 (ICI, Wilmington, DE), [^{14}C]SA—56.1 mCi/mmol (NEN Products, Boston), and skin-digesting fluid (Solvable, Packard Instrument Company, Inc., Meriden, CT).

METHODS

Briefly, the *in vitro* penetration method used is to place human cadaver skin in a diffusion chamber, apply the drug on top, and measure how much drug goes into the receptor, a buffered receptor solution, at various time points. The skin is separated into its various layers (i.e., epidermis, dermis, and receptor fluid) and the drug content is measured in the various layers.

Preparation of the skin. Fresh, excised, human skin was obtained from cadavers. Upon receipt, the skin was washed gently with 1% (v/v) aqueous dishwashing liquid, rinsed with distilled water, and patted dry with a paper towel. A 250–300-μm-thick layer of the skin was prepared with a Padgett Electrodermatome (Padgett Dermatome, Division of Kansas City Assemblage Co., Kansas City, MO). The dermatomed skin was refrigerated until used. Two hours before each experiment, the skin was placed at room temperature to equilibrate. Circular pieces of the dermatomed skin (about 12 mm in diameter) were cut with a brass punch and placed epidermis-side up on the diffusion cells.

Penetration method. The skin discs, 12-mm in diameter, were mounted on flow-through diffusion cells according to Bronough (15). The diffusion cells (Bronough design, Crown Glass Co.) were clamped, and the receptor fluid, phosphate-buffered saline (PBS) containing 1.5% Oleth and 0.01% sodium azide, was pumped through, as per Bronough (15). Unless otherwise indicated, a clinically relevant dose (5 mg/cm^2) of a sample of the formula was dispensed and spread evenly on a 0.64-cm^2 area of the skin surface using a glass rod or micropipette. The cells' temperature was maintained at 37°C throughout the experiment using a water bath/circulator (Haake, Paramus, NJ). Fraction collection

from the receptor fluid took place (rate of 1 ml per hour) at specified intervals (6, 12, 18, and 24 hours) for salicylic acid quantification throughout the experiment, using a fraction collector (Isco Retriever IV, Isco, Inc., Lincoln, NE). Samples were collected directly into scintillation vials; 10 ml of Ready Gel (Beckman, Fullerton, CA) scintillation fluid was added to each vial. The cells were left uncovered throughout the experiment. All samples were tested in seven replicates for each data point.

Skin uptake. The skin was examined for uptake of salicylic acid after 24 hours. Generally seven replicates were tested in each experiment. Before measuring uptake, the skin was wiped with two dry Q-tips® to remove unabsorbed surface material. The skin was then removed from the diffusion cells and tape-stripped one time. The stripping was assayed to determine the amount of active remaining on the skin and analyzed for drug content using a scintillation counter (Beckman Instruments Inc., Fullerton, CA). The epidermis was then separated from the dermis (by heating upside down in water 2 min at 37°C and scraping off epidermis with a Teflon spatula), and each piece of skin was digested and assayed for drug content. Digestion was performed by adding 2 ml of skin-digesting fluid and incubating the skin for 48 hours in a 40°C incubator (Precision Scientific Co., Chicago, IL). The samples were then removed, brought to room temperature, and 0.1 ml of glacial acetic acid was added to each sample. Drug content was then measured using te scintillation counter.

Analysis of penetration data: radiolabeling. Salicylic acid formulations were spiked with 1 µl/ml of [^{14}C]SA. Each microliter of [^{14}C]SA contained 1.0 µCi (designed to provide DPMs per scintillation vial in the thousands). The receptor fluid from all permeation experiments was collected directly into scintillation vials. Ten milliliters of scintillation fluid was added to each vial and all samples were analyzed in the scintillation counter. Statistical analysis of the penetration data was according to the Student *t*-test and Student Newman Keuls test.

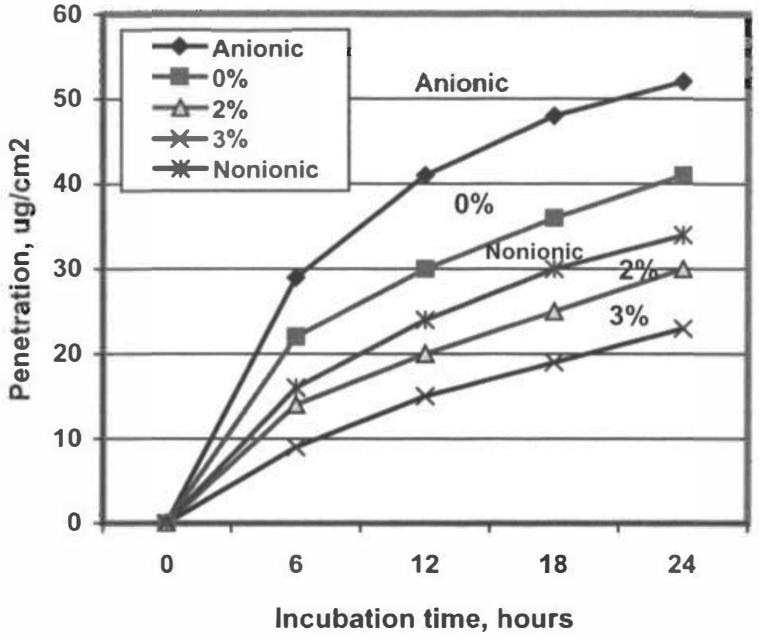
In vivo patch testing. In vivo studies were performed using a 14-day cumulative irritation patch test (16). The backs of 31 subjects were repatched daily with nine different product prototypes. Hydroalcoholic acne treatment pad juices (0.1 ml) were applied to Webril nonwoven cotton pads every day for 14 days. Irritation was also scored every day on a redness scale of 0 to 7 and on a scaling score of 0 to 3. The irritation scores of the sites were obtained daily and added to determine a final cumulative score for each product. Statistical methodology used the Friedman rank sum, and mean comparisons used the Friedman least significant difference analysis (LSD). Friedman LSD was tested at $p < 0.05$.

RESULTS

The studies are reported in two parts: (1) penetration studies to compare the effect of the polymer and other formulation components on salicylic acid delivery into various layers of the skin and (2) *in vivo* human skin irritation studies to determine the relevance of controlling the delivery of salicylic acid in various surfactant systems to the irritation potential of the topical formulations. The polyurethane polymer selected was polyol-prepolymer-15 because of its solubility in the hydroalcoholic acne treatment formulations. The results of Fares and Zatz (12) showed previously that this polymer was able to control delivery of salicylic acid to the skin due to its binding properties.

PENETRATION STUDIES

A study (Figure 1) was run with 2% salicylic acid formulations containing a hydroalcoholic, nonionic (isoceteth-20) surfactant system (formulations in Table IA) to examine the effect of polymer dose on penetration of salicylic acid from the formulation. In that study we also compared the salicylic acid penetration from the prototype nonionic surfactant formulations with and without the polymer with an anionic surfactant formulation to provide insights into the effect of the surfactants used in salicylic acid penetration. This experiment showed that addition of the polymer to the prototype nonionic system reduced the rate of delivery of the drug through the skin to the receptor fluid over the time period tested (see penetration profiles for prototypes containing 0%, 2%, and 3% polymer in Figure 1). In fact, the 0% polymer formulation delivered a significantly higher ($p \leq 0.05$) amount of drug through the skin to the receptor over the 24-hour time period than the 3% polymer-containing formulations (Table II, experiment two), and the 2% polymer-containing formulations delivered an amount of SA between the two. Results again confirm previous findings (12) that the addition of the



*All formulations contained 2% Salicylic Acid and are displayed in table 1A. Penetration was measured at 24 hours.
-Anionic is a sodium lauryl sulfate **anionic** hydroalcoholic reference formulation **without polymer**
-0% - Formula 1 is a **nonionic** Isoceteth-20 hydroalcoholic system with **0% polymer**
-2% - Formula 3 is a **nonionic** Isoceteth-20 hydroalcoholic system with **2% polymer**
-3% - Formula 4 is a **nonionic** Isoceteth-20 hydroalcoholic system with **3% polymer**
-Nonionic is a reference **nonionic** hydroalcoholic formulation also containing Isoceteth-20 (no formula analysis available)

Figure 1. Penetration of salicylic acid from nonionic vs anionic formulas through skin: Effect of polymer dose.

Table IA
Composition of 2.0% Salicylic Acid Formulations Tested

Component	Reference anionic formula	Reference nonionic formula	Formula 1	Formula 2	Formula 3	Formula 4	Formula 5	Formula 6	Formula 7	Formula 8
	Percentage of component									
Ethyl alcohol, 200 proof	42	*	42	42	42	42	42	42	42	42
Salicylic acid	2.0	2.0	2.0	2.0	2.0	2.0	2.0	2.0	2.0	2.0
Sodium lauryl sulfate	0.2									0.2
Isoceteth-20		*	0.9	0.9	0.9	0.9	0.9			
Polyol prepolymer-15				1.0	2.0	3.0	3.0	3.0		3.0
Propylene glycol	0.8									0.8
Polyethylene glycol	0.8									0.8
EDTA tetrasodium salt (36%)		*	0.05	0.05	0.05	0.05	0.05	0.05	0.05	
Triethanolamine		*	0.1	0.1	0.1	0.1		0.1	0.1	
Glycerine	5.0									5.0
Citric acid	0.3									0.3
Water	QS		QS	QS	QS	QS	QS	QS	QS	QS

* Exact amount is unknown.

Table IB
Composition of 0.5% Salicylic Acid Formulations Tested

Component	Reference anionic formula	Formula 9	Formula 10
	Percentage of component		
Ethyl alcohol, 200 proof	18	31	31
Salicylic acid	0.5	0.5	0.5
Disodium lauryl sulfosuccinate	1.5		
Isoceteth-20		0.9	0.9
Sodium lauroyl sarcosinate	0.83		
Polyolprepolymer-15			1.0
Polyethylene glycol-4	0.25		
Sodium PCA (50%)	0.8		
EDTA tetrasodium salt (36%)	0.05	0.05	0.05
Triethanolamine		0.1	0.1
Glycerine	2.5		
Water	QS	QS	QS

polymer slows the delivery of the drug through the skin in a dose-dependent fashion, even in hydroalcoholic surfactant systems.

Figure 1 directly compares salicylic acid penetration through skin into the receptor at various time points from formulations with different surfactant systems, as mentioned. These are an anionic sodium lauryl sulfate hydroalcoholic system and the isoceteth-20 nonionic prototype hydroalcoholic formulations containing 0%, 2%, and 3% polyolprepolymer-15 (see Table IA). The anionic formulation exhibited the *highest* penetration rate of salicylic acid through the skin, significantly different ($p \leq 0.05$) from all nonionic formulations at 24 hours (Table II, experiment two). This was followed by the isoceteth-20 prototype formulation with no polymer, and the lowest penetration was for formulation 4 with 3% polymer, which differed significantly from all others except formulation 3 with 2% polymer ($p \leq 0.05$). Clearly there is relatively more salicylic acid delivered to the receptor from the anionic formulation than from the nonionic formulations.

Upon addition of the polymer, the drug is released more slowly into the receptor fluid over the 24-hour period, but clearly the drug is still penetrating through the skin for up to 24 hours (Figure 1). In fact there is a consistent increase in the amount of drug penetrating through the skin at each incubation time for all product treatments. The increase in drug in the receptor is slowest for the isoceteth-20 formulation containing the highest amount of polymer (the 3% polymer formula was significantly different at the $p \leq 0.05$ level at 24 hours as compared to the anionic formula, the 0% polymer isoceteth-20 formula, and the commercial nonionic formulation, Table II). Thus the polymer effectively slows down delivery of the drug through the skin over the 24-hour period examined.

Figure 2 replots the data in Figure 1 to examine only the additional drug that has penetrated into the receptor fluid rather than total drug accumulation at each measurement time point during exposure of the skin to products. First of all, note that the maximum amount of drug that was delivered to the receptor occurred at the six-hour measurement for all formulations; by 12 hours the additional drug delivered was considerably diminished. Note that the highest maximum of salicylic acid penetration through the skin into the receptor occurred with the anionic sodium lauryl sulfate

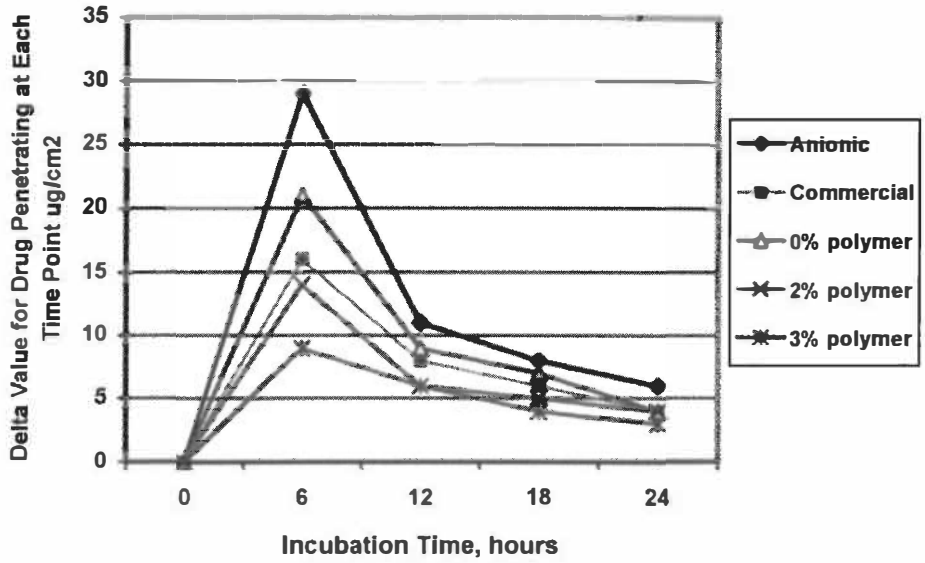
Table II
Distribution of Salicylic Acid From Various Formulations in the Epidermis, Dermis, and Receptor After Incubation for 24 Hours

Formulation	Tape strip	Epidermis	Dermis	Receptor
	μg salicyclic acid/cm^2			
Experiment one				
Reference anionic formulation	3.30 ± 0.97	16.5 ± 2.19[a]	4.49 ± 1.42	65.1 ± 2.34[b]
Reference nonionic formulation	12.1 ± 8.72	25.4 ± 5.92	4.55 ± 1.87	25.8 ± 4.65
Formulation 1	10.1 ± 4.28	22.1 ± 3.48	6.14 ± 2.12	39.6 ± 2.56[g]
Formulation 2	15.2 ± 4.42	24.4 ± 4.57	5.34 ± 2.83	32.4 ± 2.56[h]
Formulation 4	12.1 ± 6.60	37.1 ± 7.98[c]	6.69 ± 4.03	18.2 ± 3.40[i]
Formulation 5	10.3 ± 2.50	31.1 ± 7.67[d]	6.60 ± 1.62	26.6 ± 6.13
Formulation 6	10.2 ± 5.46	27.8 ± 4.20	8.68 ± 5.01	26.2 ± 4.13
Formulation 7	9.66 ± 2.55	18.5 ± 2.09[e]	5.35 ± 2.43	48.6 ± 4.21[f]
Experiment two				
Reference anionic formulation	ND	ND	ND	53.5 ± 13.3[j]
Reference nonionic formulation	ND	ND	ND	34.4 ± 7.59
Formulation 1	ND	ND	ND	41.2 ± 8.54
Formulation 3	ND	ND	ND	29.7 ± 11.0
Formulation 4	ND	ND	ND	22.6 ± 5.77[k]

Values are μg salicylic acid/cm^2. Mean ± standard deviation. ND: not done.
Statistics (all testing done at $p \leq 0.05$ by Student-Neuman-Keuls) compared within each experiment and within each part of skin:
Experiment one:
[a] Epidermal levels significantly lower compared to all other formulations except formula 7.
[b] Penetration into receptor significantly higher than for all other formulations.
[c] Epidermal levels significantly higher compared to all other formulations.
[d] Epidermal levels significantly higher compared to formulas 1, 7, and reference anionic.
[e] Epidermal levels significantly lower compared to formulas 4, 5, and 6.
[f] Penetration into receptor significantly higher compared to all other formulations except reference anionic.
[g] Penetration into receptor significantly higher compared to all other formulations except formulation 7 and reference anionic.
[h] Penetration into receptor significantly higher compared to all other formulations except formulations 1, 7, and reference anionic.
[i] Penetration into receptor significantly lower than for all other formulations.
Experiment two:
[j] Penetration into receptor significantly higher than for all other formulations.
[k] Penetration into receptor significantly lower compared to reference anionic, nonionic, and formula 1.

formulation. The nonionic formulation *without* the polymer exhibited the next highest maximum of drug penetration through the skin. When 2% polymer was incorporated, the maximum was two thirds (14 out of 21 μg/cm^2) that of the same formulation without the polymer and only about one half (14/29 or 48%) that of the anionic formula. The highest dose of polymer tested exhibited a maximum salicylic penetration that was only about one third that of the anionic. Thus all the polymer-containing nonionic formulations and even the nonionic formulation without polymer successfully reduced the initial delivery of high amounts of salicylic acid through the skin.

Delivery of the drug into the various skin layers was also examined. Figure 3 compares entrapment of salicylic acid in skin layers, again from the same isoceteth-20 formulations, with and without polymer (Table IA). What we found was that as the polymer



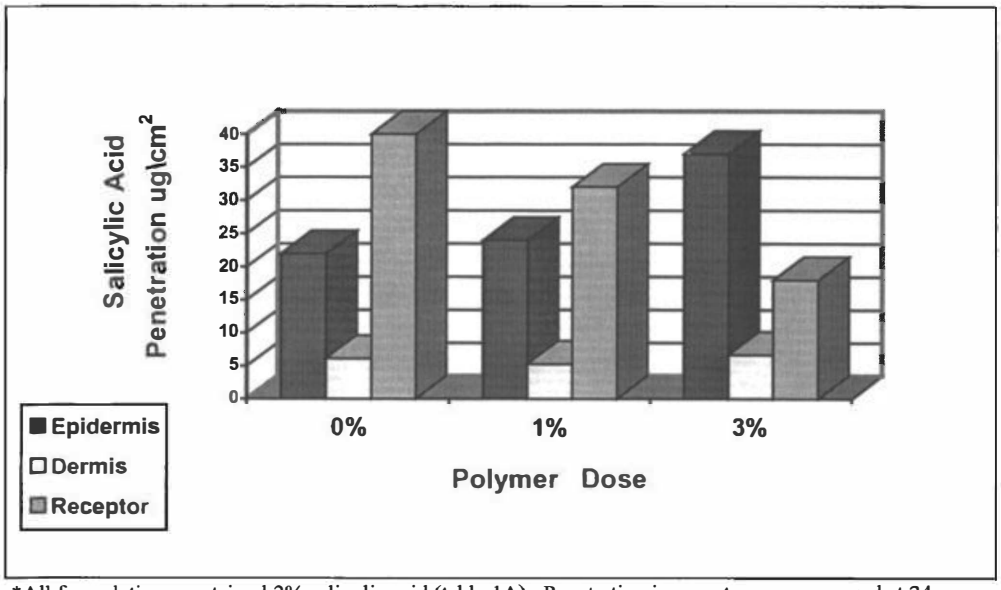
*All formulations contained 2% Salicylic Acid and are in table 1A.
-Anionic is a reference sodium lauryl sulfate hydroalcoholic formulation
-0% polymer formula 1 is the nonionic Isoceteth-20 hydroalcoholic system with **0% polymer**
-2% polymer formula 3 is the nonionic Isoceteth-20 hydroalcoholic system with **2% polymer**
-3% polymer formula 4 is the nonionic Isoceteth-20 hydroalcoholic system with **3% polymer**
-Commercial is a reference nonionic hydroalcoholic formulation (most ormulation details not available)

Figure 2. Delta values indicating amount of additional salicylic acid penetrating the receptor at each incubation time for various products: Effect of polymer dose.

dose was increased, consistently less drug was found in the receptor fluid, in agreement with the findings discussed above. However, we also found that as the polymer dose increased, more drug tended to accumulate in the epidermis [e.g., in Table II, formulation 4 with 3% polymer left significantly more ($p < 0.05$) drug in the epidermis than all other formulations in Figure 3]. Thus when the polymer is present, the drug tends to stay in the epidermis and does not penetrate through the skin as readily. The polymer is able to provide targeted delivery of the drug to the epidermal tissue rather than through the epidermis into the viable tissue where, as discussed below, it can cause increased irritation.

The phenomenon of targeted delivery was examined in another way. Table III compares the ratio of the drug in the receptor to that in the epidermis. This shows a higher ratio of drug in the receptor for the anionic formulation than for any other formulation. Results also show that the nonionic formulation with 3% polymer exhibited considerably less drug in the receptor and more in the receptor than any other formulation. This again confirms that the polymer can target salicylic acid to the epidermis, but it also indicates that the nonionic surfactant can target more drug to the epidermis as compared to the anionic formulation.

The polymer also has the same effect in the anionic surfactant formulation that it does in the nonionic isoceteth-20 type formulation. For example, in Figure 4, significantly more ($p \leq 0.05$) salicylic acid is deposited in the receptor from the formulation containing 2%



*All formulations contained 2% salicylic acid (table 1A). Penetration in receptor was measured at 24 hours.
-0% is formula 1 and is the nonionic isoceteth-20 hydroalcoholic formula with **0% polymer**
-1% is formula 2 and is the nonionic isoceteth-20 hydroalcoholic formula with **1% polymer**
-3% is formula 4 and is the nonionic isoceteth-20 hydroalcoholic formula with **3% polymer**

Figure 3. Salicylic acid penetration into the epidermis, dermis, and receptor from isoceteth-20 formulations: Effect of polymer dose.

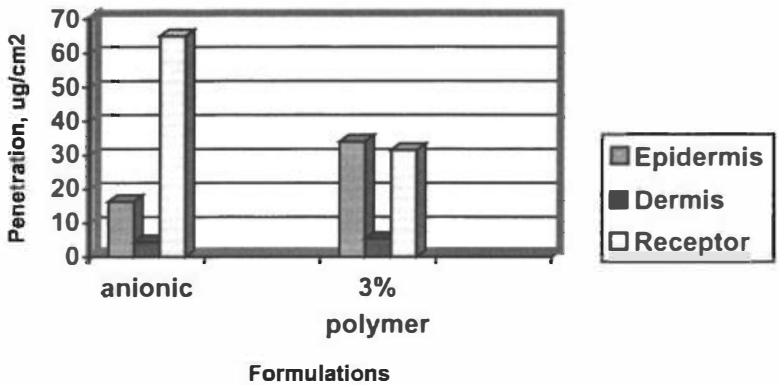
Table III
Ratio of Salicylic Acid in the Receptor to That in the Epidermis at 24 Hours in Various Hydroalcoholic Formulations

Formulation*	Ratio of salicylic acid:receptor/epidermis
Reference 2% SA anionic formula (no polymer)	2.3
Isoceteth-20 prototype with 0% polymer	1.45
Isoceteth-20 prototype with 2% polymer	1.1
Isoceteth-20 prototype with 3% polymer	0.8

* All formulations contained 2% salicylic acid and are shown in Table IA. Penetration was measured for 24 hours.
Anionic formula is shown in Table IA. Formula 1 is the nonionic isoceteth-20 system with 0% polymer. Formula 3 is the nonionic isoceteth-20 system with 2% polymer. Formula 4 is the nonionic isoceteth-20 system with 3% polymer.

salicylic acid in a sodium lauryl sulfate anionic surfactant system *without* the polymer than from the same formulation (formula 8) with 3% polymer (formulations in Table IA). Thus the polymer effect does not seem to depend on the surfactant in the system.

We also looked at the influence of three formulation ingredients in the nonionic hydroalcoholic system on the penetration of salicylic acid into various layers of the skin. The three ingredient variables were the nonionic surfactant, isoceteth-20; polyolprepolymer; and the pH adjuster, triethanolamine (TEA). Figure 5 (and Table II, experiment one) shows that formulation 4 performed the best at *minimizing* the penetration



* All formulations contained 2% salicylic acid (table 1A). Penetration was measured at 24 hours.
-Anionic is reference sodium lauryl sulfate hydroalcoholic anionic formulation with 0% polymer
-3% polymer is formula 8 and is the sodium lauryl sulfate hydroalcoholic formulation with 3% polymer

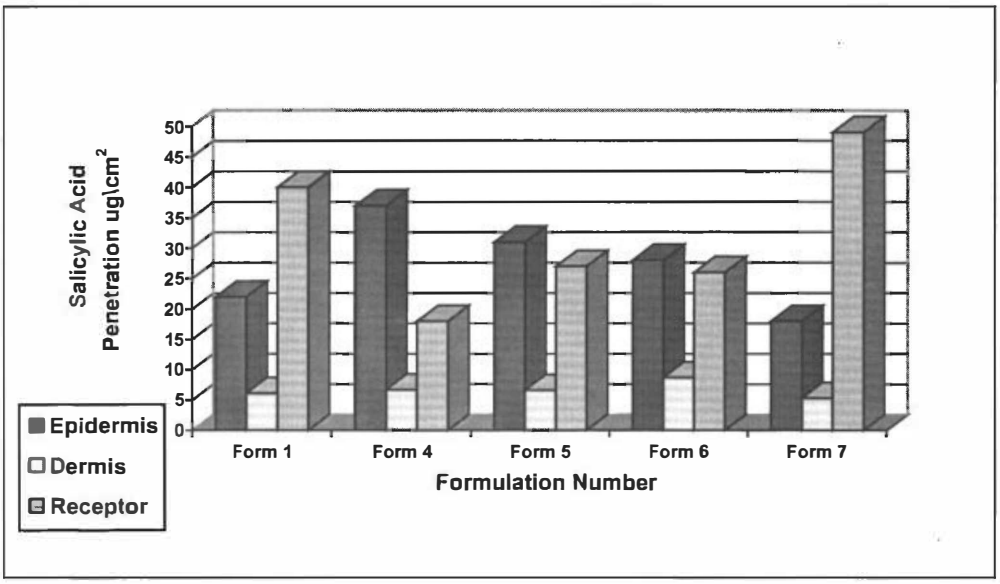
Figure 4. Penetration of salicylic acid from anionic surfactant formulations with and without polymer into the epidermis, dermis, and receptor: Effect of polymer.

rate of salicylic acid into the receptor and *maximizing* entrapment of the drug in the epidermis [it was significantly better than all other formulations at achieving this ($p \leq 0.05$)]. Three ingredients must be present to achieve this, namely isoceteth-20 surfactant, TEA, and an optimized amount of polymer (3% in this case). If any of these are deleted, such as in formulas 1 (polymer deleted), 5 (TEA deleted), 6 (isoceteth-20 deleted), and 7 (polymer and isoceteth deleted), significantly more drug goes into the receptor and less into the epidermis ($p \leq 0.05$). Thus there is a synergistic-type of relationship between these three components to target drug delivery into the epidermis and slow release into the receptor and hence through the skin.

We also compared drug penetration from the 0.5% salicylic acid prototype nonionic formulations (see Figure 6) with or without the polymer and from an anionic formulation containing 0.5% salicylic acid. Results for these low salicylic acid formulations continue to show that the polymer slows delivery of the drug through the skin (although in this case the 1% polymer effect did not quite reach statistical significance) and that the nonionic system in general is significantly better at slowing delivery of the drug through the skin than the anionic formulation ($p \leq 0.05$). The anionic system was not sodium lauryl sulfate in this case; rather, it was lauryol sarcosinate and lauryl sulfosuccinate. Still, the nonionic system surpassed the alternate anionic system in slowing delivery of salicylic acid into the skin.

IN VIVO CLINICAL PATCH TEST RESULTS

In order to determine if the polymer effect of reducing penetration of salicylic acid through the skin results in reduced irritation, we tested isoceteth-20 formulations with different levels of polymer versus no polymer versus current marketed reference formu-

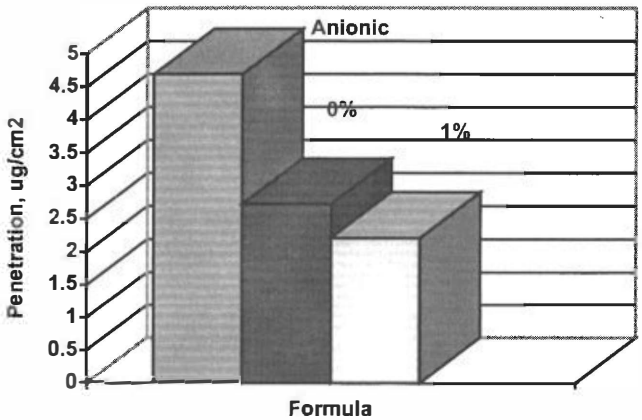


*Human skin was used as the substrate
* All formulations contained 2% salicylic acid and are shown in table 1A with the omissions shown below. Penetration in receptor was measured at 24 hours. TEA is trolamine
-Formula 4 contains isoceteth-20 formula, 3% polymer, and TEA
-Formula 1 contains isoceteth-20, TEA, but no polymer
-Formula 5 contains the isoceteth-20, 3% polymer minus TEA
-Formula 6 is minus isoceteth-20 but contains 3% polymer and TEA
-Formula 7 is minus isoceteth-20 formula minus polymer but contains TEA

Figure 5. Salicylic acid penetration into the epidermis, dermis, and receptor from isoceteth-20 formulations: Synergic effect of polymer and formulation ingredients.

lations. We were also interested in comparing the isoceteth system with other surfactant systems. A 14-day cumulative irritation patch test was run on nine formulations. Both 2% salicylic acid and 0.5% salicylic acid formulations were examined. The results are displayed in Table IV.

Results show that all 2% salicylic acid nonionic formulations containing 2% and 3% polymer were significantly ($p \leq 0.05$) milder than the nonionic prototype without polymer. The anionic formulation with sodium lauryl sulfate was the most aggressive to the skin and significantly worse ($p \leq 0.05$) than any other formulation tested. The 2% nonionic isoceteth-20 salicylic formulations were the mildest and even milder than the 0.5% salicylic acid reference anionic surfactant formulation. Thus the amount of salicylic acid in the formulation is not the predominant factor controlling irritation; rather, it appears to be the surfactant system. This is due to the aggressive nature of the anionic surfactant system used and also to the lack of a sufficient surfactant micellar content in the formulation (or on the skin surface after the alcohol has evaporated) to retard drug flow through the skin and minimize the concentration of surfactant monomer. Thus, overall the clinical results validate that both the slow release of salicylic acid through the skin, presumably controlled by the polymer, and the change to a milder nonionic surfactant TEA system, appear to translate into reduced irritation.



*Formulations are in table 1B. Penetration was measured at 24 hours
-Anionic system is 0.5% salicylic acid reference formulation without polymer
-0% polymer - formula 9 is the nonionic isoceteth-20 system with 0.5% SA and 0% polymer
-1% polymer - formula 10 is the nonionic isoceteth-20 system with 0.5% SA and 1% polymer

Figure 6. Penetration of 0.5% salicylic acid into the receptor: Effect of polymer dose and comparison to reference products.

Table IV
14-Day Cumulative Irritation Potential of Several Hydroalcoholic Solutions[a]

Hydroalcoholic acne treatment formulations[b]	Irritation score[c]
2% Salicylic acid; 0% polyolprepolymer; nonionic isoceteth-20 (formulation 1)	223
2% Salicylic acid; 2% polyolprepolymer; nonionic isoceteth-20 (formulation 3)	182
2% Salicylic acid; 3% polyolprepolymer; nonionic isoceteth-20 (formulation 4)	193
0.5% Salicylic acid; 0% polyolprepolymer; nonionic isoceteth-20 (formulation 9)	88
0.5% Salicylic acid; 1% polyolprepolymer; nonionic isoceteth-20 (formulation 10)	73
0.5% Salicylic acid commercial anionic formulation	338
2% Salicylic acid commercial anionic formulation	Extreme irritation, pulled off test
Test control (water/sodium chloride)	24

[a] 14-day patch test sum of daily irritation scores.
[b] Formulations in Tables IA or IB.
[c] Statistical differences in test samples are discussed in the text.

DISCUSSION

The hydroalcoholic formulations studied contain a very mild nonionic surfactant, isoceteth-20. Nonionic surfactants are perhaps the mildest of all surfactant systems to human skin (17,18), and our irritation studies reported herein support this finding. Like other surfactants, they also micellize (self-associate) in solution at a low concentration and can trap salicylic acid in their micellar or vesicular reservoir. (The micellar or vesicular reservoir may be formed on the skin surface after alcohol evaporation, as the presence of alcohol in the solution may not allow micellization to occur.) As a result, salicylic acid will penetrate more slowly into and through the skin rather than as a large

dose after the initial exposure. These formulations also incorporate the nonionic polyurethane polymer, polyolprepolymer-15. Both of these excipients tend to associate with the salicylic acid drug via weak hydrophobic bonds and alter the "activity" of the drug and the penetration profile of the drug into and through the skin. This results in slow release of the drug and targeted delivery into the epidermis rather than through the skin. Reduction of the initial rapid rate of delivery of the drug into the receptor parallels the reduction of irritation found in the cumulative irritation test.

However, even the nonionic hydroalcoholic formulations without the polymer are milder than the marketed reference formulations containing anionic surfactants. Because of the absence of a charge in the nonionic surfactants, they do not dissociate/denature the stratum corneum as readily as certain anionics (17,18). This confirms that the surfactant type is the key factor dictating the enhanced mildness of the surfactant systems and suggests that the increased micellar or vesicular reservoir characteristic of systems with a lower critical micelle concentration (as is the case of these nonionic versus anionic surfactants) may explain in part the reduced irritancy of the system. This presumably occurs by greater entrapment of salicylic acid in the micellar reservoir and by minimizing the surfactant monomer available to attack the skin barrier, since most of the surfactant is tied up in the micelle (17,18). Arguably, the surfactant micellization or vesicle formation may occur on the skin surface after the alcohol has evaporated. The importance of surfactant type is further substantiated by the fact that a reference (commercial) anionic formulation with 0.5% salicylic acid was substantially more irritating than any nonionic surfactant system with 2% salicylic acid. Yet the anionic formulation with 0.5% salicylic acid delivered the least amount of salicylic acid of the two (comparing Figure 6 with the other figures, for the 2% nonionic formulations, although comparing results between different experiments is not entirely reliable). Thus the surfactant type rather than the concentration of salicylic acid is the predominant factor controlling irritancy.

One other explanation for the findings is in order. It is possible that the predominant effect of slowing down delivery of salicylic acid by the surfactant systems could be due to competition for binding surfaces on the stratum corneum. Such surfaces are hydrophobic in nature, a fact that is well published, and the hydrophobic part of the surfactants could adsorb to these regions of the keratin, thus preventing the salicylic acid from binding to these same sites. However, the relationship between binding to keratin and penetration of salicylic acid is unclear. An interesting experiment would be to assess the relationship of salicylic acid delivery to the dose of the surfactant both above and below the critical micelle concentration of the surfactant. It would also be interesting to isolate micelles or vesicles after alcohol evaporation and determine the extent of entrapment of salicylic acid into these structures [see review by Rhein (17,18)].

Alcohol could also be a contributor to the irritancy. However, the findings suggest this is not the case. The low-alcohol (18%) commercial formulations with 0.5% salicylic acid in an anionic surfactant system were more irritating than the 42% alcohol formulations containing 2% salicylic acid and the nonionic surfactant. Alcohol does not seem to play a major role in controlling the irritation except for the initial solubilization of the salicylic acid.

The learnings from these studies are that polyolprepolymer-15 and isoceteth-20 can be used to target the delivery of salicylic acid preferentially to the epidermis and diminish the rate of penetration through the skin into the receptor, which would be the blood-

stream in an *in vivo* situation. TEA also appears to enhance entrapment of salicylic acid in the epidermis (see Figure 5 comparing formulations 4 and 5). The salicylic acid, to some extent, is present as the TEA salt, which is a pseudononionic, hydrophobic species. This species will favor interaction with the hydrophobic surfactant micelle and the hydrophobic regions of the polymer. In the absence of the surfactant and polymer (see formula 7 in Figure 5), the TEA salicylate along with the undissociated salicylic acid presumably penetrate very readily into the skin, presumably through the hydrophobic lipid regions of the stratum corneum. When present in the formulation, the isoceteth-20 surfactant and the polyolprepolymer both alternatively interact with the TEA salt of salicylic acid, as well as with salicylic acid via hydrophobic bonds, and delay their penetration into the stratum corneum; the TEA salt seems to interact more efficiently, however.

The remaining question is whether altering the delivery of salicylic acid to target the epidermis changes the efficacy of the drug in treating acne. No studies were done comparing the nonionic polymeric hydroalcoholic solution with the anionic system. It is felt that acne is a disease of the pilosebaceous unit and that the epidermis becomes hyperkeratotic. This leads to the blockage of the unit and proliferation of the *P. acnes* in the unit. Targeting salicylic acid to the epidermis of the unit would likely be optimal for the treatment of acne and for minimizing the irritation that seems to evolve from further drug penetration past the epidermis and into the cutaneous microvasculature.

CONCLUSIONS

Several conclusions can be derived from the current studies as follows:

- Changing from the anionic to the nonionic (isoceteth-20) surfactant system for the hydroalcoholic solution slows down release/delivery of salicylic acid through the skin into the receptor during a 24-hour time period, thereby reducing the rate of penetration.
- Adding the hydrophobic, nonionic polyolprepolymer-15 to the hydroalcoholic surfactant systems in a dose-dependent fashion reduces the rate of delivery of the drug through the skin to the receptor during the 24-hour period measured.
- The reduced rate of delivery of the drug to the receptor parallels accumulation of drug in the epidermis; thus these systems can be used to target salicylic acid preferentially to the epidermis.
- A synergistic relationship exists between three components, namely nonionic surfactant, hydrophobic polymer, and triethanolamine, which maximizes the benefit of slow release of salicylic acid and accumulation of the drug in the epidermis significantly over each alone or in pairs.
- The synergistic nonionic system of polymer, nonionic surfactant, and triethanolamine reduces the initial large dose (and hence the rate) of salicylic acid passing through skin, as is seen with anionic hydroalcoholic systems; this occurred in a dose-dependent fashion with the addition of polymer.
- The cumulative irritation test verified that the nonionic polymer hydroalcoholic system is significantly milder than the anionic hydroalcoholic systems and that the addition of polyolprepolymer reduced irritation in a dose-dependent fashion.
- Formulations that targeted delivery of salicylic acid to the epidermis and reduced the rate of penetration through skin were generally milder and often significantly so, depending on dose of polymer and the surfactant type.

- Surfactant structure rather than dose of salicylic acid is the predominant factor controlling irritancy of these hydroalcoholic formulations, since anionic formulations (reference formulations) with reduced doses of salicylic acid (0.5%) are still some of the most irritating formulations tested. Doses of salicylic acid (and alcohol) were secondary.

Thus the idea of optimizing the slow release of the drug and targeting delivery of the drug into the epidermis while minimizing penetration through the skin translates into lower-irritation formulations to treat acne. Incorporation of hydrophobic polymers enables slower delivery of the hydrophobic drug. Additionally, formulating with milder nonionic surfactants with low critical micelle concentrations that produce a large reservoir of micelles to trap salicylic acid (either in solution or on the skin surface) provides a less aggressive and reduced level of surfactant monomer, helping to achieve that endpoint. An additional chemical strategy of keeping salicylic acid in the form of a pseudononionic TEA salt also enhances entrapment of the drug in the nonionic polymer vehicle and delays delivery through the skin, resulting in enhanced mildness.

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