Effect of Nonionic Surfactants on Percutaneous Absorption of Salicylic Acid and Sodium Salicylate in the Presence of Dimethyl Sulfoxide

WU-WEI SHEN *, AUGUST G. DANTI ˣ, and FRANK N. BRUSCATO

Abstract □ Fifteen nonionic surfactants, 10% (w/w), were each incorporated into white petrolatum USP ointment base containing 10% (w/w) salicylic acid or 11.6% (w/w) sodium salicylate with 10% (w/w) dimethyl sulfoxide. Percutaneous absorption was determined from blood salicylate levels in New Zealand white rabbits at regular intervals for 8 hr following application of the ointment. Percutaneous absorption of salicylic acid was increased significantly when sorbitan monopalmitate, sorbitan trioleate, poloxamer 231, poloxamer 182, polyoxyethylene 4 lauryl ether, polyoxyethylene 2 oleyl ether, or polyoxyl 8 stearate was added to the ointment containing dimethyl sulfoxide, salicylic acid, and white petrolatum. Percutaneous absorption of sodium salicylate was increased significantly when sorbitan monolaurate, sorbitan monopalmitate, or poloxamer 182 was added to the ointment containing dimethyl sulfoxide, sodium salicylate, and white petrolatum.

Keyphrases □ Surfactants, nonionic—effect on percutaneous absorption of salicylic acid and sodium salicylate from ointment bases containing dimethyl sulfoxide, rabbits □ Absorption, percutaneous—salicylic acid and sodium salicylate from ointment bases containing dimethyl sulfoxide, effect of nonionic surfactants, rabbits □ Salicylic acid—percutaneous absorption from ointment bases containing dimethyl sulfoxide, effect of nonionic surfactants, rabbits □ Sodium salicylate—percutaneous absorption from ointment bases containing dimethyl sulfoxide, effect of nonionic surfactants, rabbits □ Petrolatum, white—ointment base, percutaneous absorption of salicylic acid and sodium salicylate, effect of nonionic surfactants □ Ointment bases—white petrolatum, percutaneous absorption of salicylic acid and sodium salicylate, effect of nonionic surfactants

Dimethyl sulfoxide has demonstrated a broad spectrum of activities, including the enhancement of penetration through plant and animal membranes (1). It has been suggested for possible use as an analgesic agent, anti-inflammatory adjunct, bacteriostatic agent, diuretic, tranquilizer, potentiator of other compounds, and penetrant carrier (2). Dimethyl sulfoxide facilitates the transport of sodium salicylate, sulfadiazine sodium, aminophylline, Evans blue dye, and heparin sodium across the mucous membrane of a dog's bladder (3). Kligman (1) concluded from his experimentation that, if dimethyl sulfoxide is to be clinically useful, quite concentrated solutions, perhaps 80–90%, would be required to accelerate the rate of topical medicaments such as corticosteroids through the skin. Dimethyl sulfoxide enhanced the percutaneous absorption of salicylic acid from hydrophilic ointment USP and hydrophilic petrolatum USP (4).

In November 1965, dimethyl sulfoxide was removed from the market by the Food and Drug Administration because it was reported to have a possible harmful effect on human eyes. The lens of eyes of dimethyl sulfoxide-treated animals were characterized by division into two zones, a central area stimulating a lens nucleus and a peripheral area (5).

The mechanism of increased membrane permeability effected by dimethyl sulfoxide is essentially unknown. It was pointed out that the carrier mechanism produced by dimethyl sulfoxide might be related to the fact that it forms complexes with various substances (2). The attraction of dimethyl sulfoxide for water should be considered as a possible factor in altered membrane permeability.

Since enhanced percutaneous absorption of drugs can be achieved *via* dimethyl sulfoxide (4), substances possessing a particular affinity for the membranous structure may contribute to the overall enhancement. Such substances are classified as surface-active agents. Of the three major surface-active agents, a nonionic surfactant can possibly emulsify the sebum, enhance the thermodynamic activity of drugs, or change the diffusion constant and activity coefficient of drugs (6), consequently permitting drugs to penetrate into the cells easily.

This study determined the effects of selected nonionic surfactants on the percutaneous absorption of salicylic acid and sodium salicylate in white petrolatum USP with dimethyl sulfoxide.

EXPERIMENTAL

The following ointments were used: 10% (w/w) salicylic acid[1] in white petrolatum[2], 11.6% (w/w) sodium salicylate[3] in white petrolatum, 10% (w/w) dimethyl sulfoxide[4] plus 10% (w/w) salicylic acid in white petrolatum, 10% (w/w) dimethyl sulfoxide plus 11.6% (w/w) sodium salicylate in white petrolatum, 10% (w/w) surfactant plus 10% (w/w) salicylic acid plus 10% (w/w) dimethyl sulfoxide in white petrolatum, and 10% (w/w) surfactant plus 11.6% (w/w) sodium salicylate plus 10% (w/w) dimethyl sulfoxide in white petrolatum.

The property of absorption was compared between an ointment consisting of 10% (w/w) dimethyl sulfoxide plus 10% (w/w) salicylic acid in white petrolatum and one containing 10% (w/w) surfactant plus 10% (w/w) salicylic acid plus 10% (w/w) dimethyl sulfoxide in white petrolatum. This comparison was repeated with sodium salicylate replacing the salicylic acid.

Surfactants—The nonionic surfactants selected [and hydrophilic–lipophilic balance (HLB) values] were poloxamer 231[5] (2), poloxamer 182[6] (7), poloxamer 184[7] (15), polyoxyethylene 20 oleyl ether[8] (15.3), polyoxyethylene 4 lauryl ether[9] (9.5), polyoxyethylene 2 oleyl ether[10] (4.9), sorbitan monolaurate[11] (8.6), sorbitan monopalmitate[12] (6.7), sorbitan trioleate[13] (1.8), polysorbate 20[14] (16.7), polysorbate 40[15] (15.6), polysorbate 60[16] (14.9), polyoxyl 8 stearate[17]

[1] USP grade, lot 61416, Merck & Co.
[2] USP grade, lot 731214, Fisher Scientific.
[3] USP grade, lot 71610, Merck & Co.
[4] Experimental drug grade, lot 50509, Crown Zellerbach.
[5] Pluronic L81, Wyandotte Chemical Corp., Wyandotte, Mich.
[6] Pluronic L62, Wyandotte Chemical Corp., Wyandotte, Mich.
[7] Pluronic L64, Wyandotte Chemical Corp., Wyandotte, Mich.
[8] Brij 99, Atlas Chemical Industries, Wilmington, Del.
[9] Brij 30, Atlas Chemical Industries, Wilmington, Del.
[10] Brij 93, Atlas Chemical Industries, Wilmington, Del.
[11] Span 20, Atlas Chemical Industries, Wilmington, Del.
[12] Span 40, Atlas Chemical Industries, Wilmington, Del.
[13] Span 85, Atlas Chemical Industries, Wilmington, Del.
[14] Tween 20, Atlas Chemical Industries, Wilmington, Del.
[15] Tween 40, Atlas Chemical Industries, Wilmington, Del.
[16] Tween 60, Atlas Chemical Industries, Wilmington, Del.
[17] Myrj 45, Atlas Chemical Industries, Wilmington, Del.

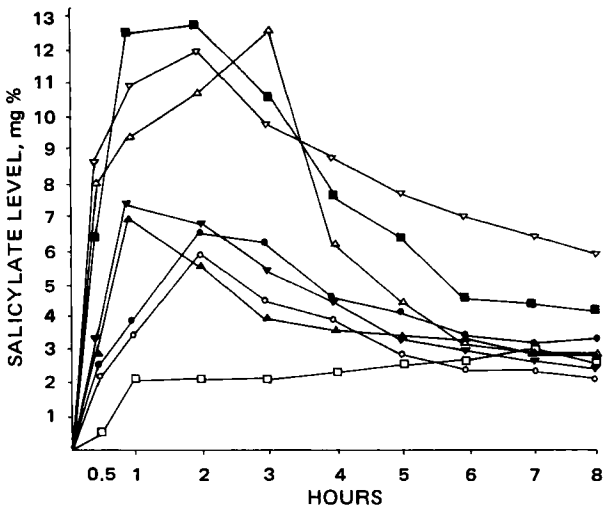

Figure 1—*Effect of sorbitan and polysorbate surfactants on percutaneous absorption of salicylic acid in the presence of dimethyl sulfoxide. Key: △, 10% sorbitan monolaurate plus 10% dimethyl sulfoxide plus 10% salicylic acid; ▽, 10% sorbitan monopalmitate plus 10% dimethyl sulfoxide plus 10% salicylic acid; ■, 10% sorbitan trioleate plus 10% dimethyl sulfoxide plus 10% salicylic acid; ●, 10% polysorbate 20 plus 10% dimethyl sulfoxide plus 10% salicylic acid; ▲, 10% polysorbate 40 plus 10% dimethyl sulfoxide plus 10% salicylic acid; ▼, 10% polysorbate 60 plus 10% dimethyl sulfoxide plus 10% salicylic acid; ○, 10% dimethyl sulfoxide plus 10% salicylic acid; and □, 10% salicylic acid.*

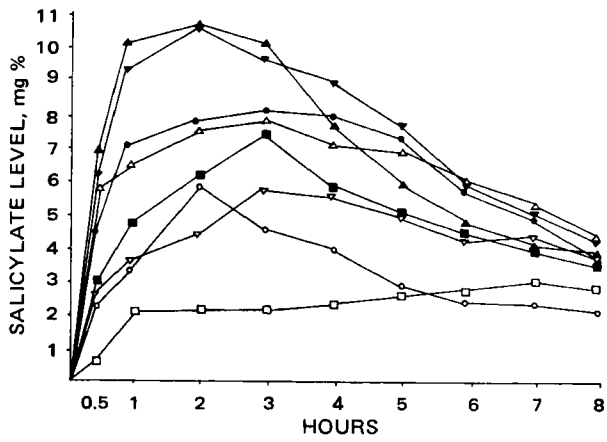

Figure 3—*Effect of polyoxyethylene esters and mixed surfactants on percutaneous absorption of salicylic acid in the presence of dimethyl sulfoxide. Key: △, 10% polyoxyl 8 stearate plus 10% dimethyl sulfoxide plus 10% salicylic acid; ▽, 10% polyoxyethylene 30 monostearate plus 10% dimethyl sulfoxide plus 10% salicylic acid; ■, 10% polyoxyethylene 40 monostearate plus 10% dimethyl sulfoxide plus 10% salicylic acid; ●, 5% sorbitan trioleate plus 5% polysorbate 40 plus 10% dimethyl sulfoxide plus 10% salicylic acid; ▲, 5% polyoxyethylene 2 oleyl ether plus 5% polyoxyethylene 20 oleyl ether plus 10% dimethyl sulfoxide plus 10% salicylic acid; ▼, 5% polyoxyl 8 stearate plus 5% polyoxyethylene 40 monostearate plus 10% dimethyl sulfoxide plus 10% salicylic acid; ○, 10% dimethyl sulfoxide plus 10% salicylic acid; and □, 10% salicylic acid.*

(11.1), polyoxyethylene 30 monostearate[18] (16), and polyoxyethylene 40 monostearate[19] (16.9).

To investigate the effect of the HLB value on percutaneous absorption of salicylic acid and sodium salicylate, the following matched surfactants were used: 5% (w/w) sorbitan trioleate plus 5% (w/w) polysorbate 40 with an HLB of 8.7, 5% (w/w) polyoxyethylene 20 oleyl ether plus 5% (w/w) polyoxyethylene 2 oleyl ether with an HLB of 10.1, and 5% (w/w) polyoxyl 8 stearate plus 5% (w/w) polyoxyethylene 40 monostearate with an HLB of 14.0.

Ointment Preparation—Salicylic acid and sodium salicylate, previously reduced to fine powders in a ball mill, were each passed through an 80-mesh sieve and dried at 50° in a heated vacuum desiccator for at least 48 hr before use. The ointments prepared contained 10% (w/w) milled salicylic acid or 11.6% (w/w) milled sodium salicylate, 10% (w/w) surfactant, and 10% (w/w) dimethyl sulfoxide. Each ingredient was accurately weighed[20] and incorporated into the white petrolatum.

Test Animals—Each ointment was applied to a New Zealand white rabbit, 3.0–4.0 kg, randomly selected without regard to sex. Each rabbit was used only three times and received the same surfactant in each test. Only one pair of rabbits was utilized during any one ex-

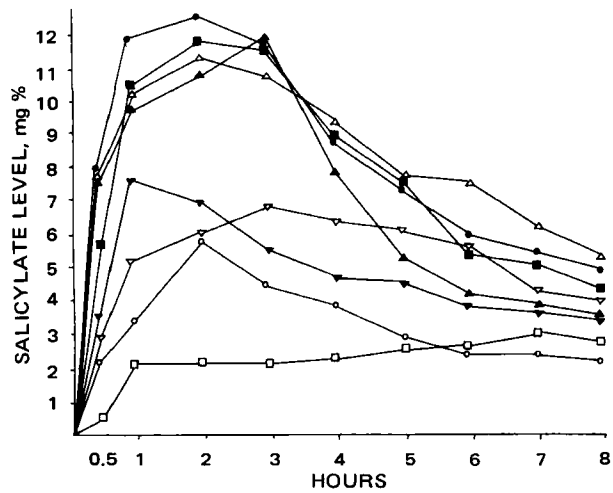

Figure 2—*Effect of poloxamer and polyoxyethylene surfactants on percutaneous absorption of salicylic acid in the presence of dimethyl sulfoxide. Key: △, 10% poloxamer 182 plus 10% dimethyl sulfoxide plus 10% salicylic acid; ▽, 10% poloxamer 184 plus 10% dimethyl sulfoxide plus 10% salicylic acid; ■, 10% poloxamer 231 plus 10% dimethyl sulfoxide plus 10% salicylic acid; ●, 10% polyoxyethylene 2 oleyl ether plus 10% dimethyl sulfoxide plus 10% salicylic acid; ▲, 10% polyoxyethylene 4 lauryl ether plus 10% dimethyl sulfoxide plus 10% salicylic acid; ▼, 10% polyoxyethylene 20 oleyl ether plus 10% dimethyl sulfoxide plus 10% salicylic acid; ○, 10% dimethyl sulfoxide plus 10% salicylic acid; and □, 10% salicylic acid.*

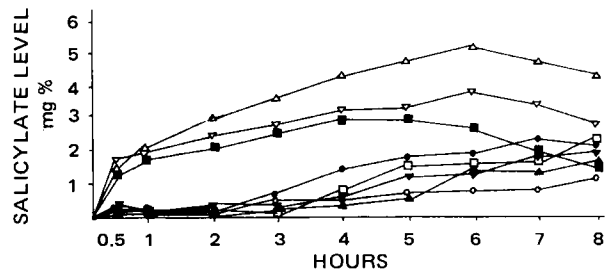

Figure 4—*Effect of sorbitan and polysorbate surfactants on percutaneous absorption of sodium salicylate in the presence of dimethyl sulfoxide. Key: △, 10% sorbitan monolaurate plus 10% dimethyl sulfoxide plus 11.6% sodium salicylate; ▽, 10% sorbitan monopalmitate plus 10% dimethyl sulfoxide plus 11.6% sodium salicylate; ■, 10% sorbitan trioleate plus 10% dimethyl sulfoxide plus 11.6% sodium salicylate; ●, 10% polysorbate 20 plus 10% dimethyl sulfoxide plus 11.6% sodium salicylate; ▲, 10% polysorbate 40 plus 10% dimethyl sulfoxide plus 11.6% sodium salicylate; ▼, 10% polysorbate 60 plus 10% dimethyl sulfoxide plus 11.6% sodium salicylate; ○, 10% dimethyl sulfoxide plus 11.6% sodium salicylate; and □, 11.6% sodium salicylate.*

[18] Myrj 51, Atlas Chemical Industries, Wilmington, Del.
[19] Myrj 52, Atlas Chemical Industries, Wilmington, Del.
[20] Harvard Trip Balance, Ohaus, N.J.

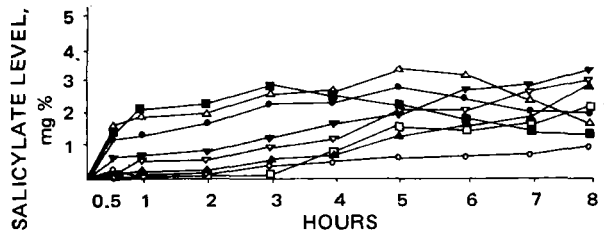

Figure 5—*Effect of polyoxyethylene and poloxamer surfactants on percutaneous absorption of sodium salicylate in the presence of dimethyl sulfoxide. Key: △, 10% poloxamer 182 plus 10% dimethyl sulfoxide plus 11.6% sodium salicylate; ▽, 10% poloxamer 184 plus 10% dimethyl sulfoxide plus 11.6% sodium salicylate; ■, 10% poloxamer 231 plus 10% dimethyl sulfoxide plus 11.6% sodium salicylate; ●, 10% polyoxyethylene 2 oleyl ether plus 10% dimethyl sulfoxide plus 11.6% sodium salicylate; ▲, 10% polyoxyethylene 4 lauryl ether plus 10% dimethyl sulfoxide plus 11.6% sodium salicylate; ▼, 10% polyoxyethylene 20 oleyl ether plus 10% dimethyl sulfoxide plus 11.6% sodium salicylate; ○, 10% dimethyl sulfoxide plus 11.6% sodium salicylate; and □, 11.6% sodium salicylate.*

perimental period due to space and time limitations. A 7-day rest period was allowed before reapplication of the ointment.

The animals were maintained on rabbit chow[21] and water and housed individually in an animal room maintained at 25°. Twenty-four hours prior to the application of the ointment to the rabbit, hair was removed from the ears and the dorsal area between the forelegs and hindlegs on both sides of the spine (4) with an animal clipper and a depilatory cream[22].

Application of Ointment—A specially prepared bandage restricted and controlled the area of contact between the rabbit and the ointment. The edges of an 8.4 × 14.7-cm^2 piece of aluminum foil were doubled over and flattened 1 cm on each side to produce a rectangular plate measuring 6.4 × 12.7 cm^2 with 1-cm reinforced margin. A 5.0-g sample of the selected ointment was uniformly spread over one surface of the plate, whose opposite side was centered on an 8.9 × 20-cm^2 strip of adhesive tape. The entire assembly was then applied to the shaved dorsal skin of the rabbit and adjusted to conform to contours of the area.

The assembly was covered with a bandage to ensure adequate contact between the ointment and the skin to minimize the possibility of contamination. The bandage arrangement was adapted from Stolar *et al.* (7). The ointment remained in contact with the skin for 8 hr, during which time the rabbit did not receive food or water.

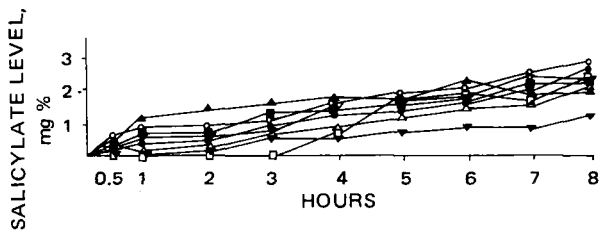

Figure 6—*Effect of polyoxyethylene esters and mixed surfactants on percutaneous absorption of sodium salicylate in the presence of dimethyl sulfoxide. Key: △, 10% polyoxyl 8 stearate plus 10% dimethyl sulfoxide plus 11.6% sodium salicylate; ▽, 10% polyoxyethylene 30 monostearate plus 10% dimethyl sulfoxide plus 11.6% sodium salicylate; ■, 10% polyoxyethylene 40 monostearate plus 10% dimethyl sulfoxide plus 11.6% sodium salicylate; ●, 5% sorbitan trioleate plus 5% polysorbate 40 plus 10% dimethyl sulfoxide plus 11.6% sodium salicylate; ▲, 5% polyoxyethylene 2 oleyl ether plus 5% polyoxyethylene 20 oleyl ether plus 10% dimethyl sulfoxide plus 11.6% sodium salicylate; ▼, 5% polyoxyl 8 stearate plus 5% polyoxyethylene 40 monostearate plus 10% dimethyl sulfoxide plus 11.6% sodium salicylate; ○, 10% dimethyl sulfoxide plus 11.6% sodium salicylate; and □, 11.6% sodium salicylate.*

[21] Purina.
[22] Surgex, Ciba, Summit, N.J.

Table I—*t* Test Value from the Comparison of the Overall Average of Percutaneous Salicylate Absorption from the Rabbit between Surfactant (S) plus Salicylic Acid (I) plus White Petrolatum USP (II) and Salicylic Acid plus White Petrolatum USP Ointments and also between Dimethyl Sulfoxide (III) plus Salicylic Acid plus White Petrolatum USP and Dimethyl Sulfoxide plus Surfactant plus Salicylic Acid plus White Petrolatum USP Ointments

Surfactant	*t* Value between I + II and S + I + II	*t* Value between III + S + I + II and III + I + II
Poloxamer 231	4.905[a]	3.886[a]
Poloxamer 182	4.050[a]	5.737[a]
Poloxamer 184	2.992[a]	2.960[a]
Polyoxyethylene 20 oleyl ether	2.461[a]	2.112[a]
Polyoxyethylene 4 lauryl ether	3.154[a]	2.944[a]
Polyoxyethylene 2 oleyl ether	5.918[a]	3.245[a]
Sorbitan monolaurate	3.038[a]	4.537[a]
Sorbitan monopalmitate	11.308[a]	9.877[a]
Sorbitan trioleate	5.435[a]	9.014[a]
Polysorbate 20	2.104[a]	1.165[b]
Polysorbate 40	2.385[a]	0.745[b]
Polysorbate 60	2.886[a]	0.937[b]
Polyoxyl 8 stearate	2.815[a]	3.972[a]
Polyoxyethylene 30 monostearate	1.901[a]	2.164[a]
Polyoxyethylene 40 monostearate	1.851[a]	3.669[a]
Sorbitan trioleate plus polysorbate 40	3.784[a]	3.804[a]
Polyoxyethylene 20 oleyl ether plus polyoxyethylene 2 oleyl ether	4.846[a]	4.226[a]
Polyoxyl 8 stearate plus polyoxyethylene 40 monostearate	3.380[a]	3.879[a]

[a] Significant difference at 95% level. [b] No significant difference.

Sample Collection Procedure—Blood samples were withdrawn, and the plasma salicylate concentration was determined. One-half milliliter of blood was withdrawn from the marginal ear vein of the rabbit at the following time periods: prior to application of ointment, 0.5 hr after ointment application, and at hourly intervals for 8 hr after application of the ointment. Blood samples were collected in 1-ml sterile disposable 26-gauge tuberculin syringes[23], 1.27 cm containing 0.1 ml of heparin sodium[24]. This blood and heparin mixture was added to 5.0 ml of the combined protein color reagent in a centrifuge tube and analyzed for salicylate content according to the method described by Trinder (8).

After centrifugation and filtration, the colorimetric analysis for salicylate was performed at a wavelength of 540 nm using a spectrophotometer[25]. The absorbance reading obtained from the blood sample withdrawn prior to application was considered the zero reading and subtracted from the other reading to account for the absorbance contributed by other blood constituents. The salicylate content was obtained from a curve previously drawn by using 0.1 ml of heparin sodium and 0.5 ml of sodium salicylate solutions containing the equivalent of 1, 5, 10, 15, and 20 mg % of salicylic acid with 5.0 ml of coloring reagent.

Statistical Analysis of Data—Three replications were run in each individual test. A *t* test with two degrees of freedom at the 95% significance level was used to test the null hypothesis.

[23] Plastipak, Becton, Dickinson & Co., Rutherford, N.J.
[24] USP grade, lot 3AK90A, 10,000 units/ml, Eli Lilly.
[25] Beckman DT-DB model 95.

Table II—t Test Value from the Comparison of the Overall Average of Percutaneous Salicylate Absorption from the Rabbit between Surfactant (S) plus Sodium Salicylate (IV) plus White Petrolatum USP (II) and Sodium Salicylate plus White Petrolatum USP Ointments and also between Dimethyl Sulfoxide (III) plus Sodium Salicylate plus White Petrolatum USP and Dimethyl Sulfoxide plus Surfactant plus Sodium Salicylate plus White Petrolatum USP Ointments

Surfactant	t Value from IV + II and S + IV + II	t Value from III + IV + II and III + S + IV + II
Poloxamer 231	2.011[a]	1.996[a]
Poloxamer 182	3.189[a]	1.645[b]
Poloxamer 184	4.258[a]	1.687[b]
Polyoxyethylene 20 oleyl ether	4.084[a]	2.246[a]
Polyoxyethylene 4 lauryl ether	2.556[a]	2.961[a]
Polyoxyethylene 2 oleyl ether	1.582[b]	3.011[a]
Sorbitan monolaurate	3.858[a]	4.365[a]
Sorbitan monopalmitate	1.878[a]	3.614[a]
Sorbitan trioleate	2.237[a]	3.564[a]
Polysorbate 20	6.209[a]	3.548[a]
Polysorbate 40	4.923[a]	3.854[a]
Polysorbate 60	4.289[a]	3.123[a]
Polyoxyl 8 stearate	3.458[a]	2.843[a]
Polyoxyethylene 30 monostearate	5.464[a]	2.853[a]
Polyoxyethylene 40 monostearate	5.614[a]	2.964[a]
Sorbitan trioleate plus polysorbate 40	3.460[a]	3.224[a]
Polyoxyethylene 20 oleyl ether plus polyoxyethylene 2 oleyl ether	4.162[a]	2.765[a]
Polyoxyl 8 stearate plus polyoxyethylene 40 monostearate	6.040[a]	2.367[a]

[a]Significant difference at 95% level. [b]No significant difference.

RESULTS

The altered percutaneous absorption patterns of salicylic acid and sodium salicylate obtained upon addition of selected surfactants to 10% (w/w) salicylic acid plus 10% (w/w) dimethyl sulfoxide in white petrolatum USP or to 11.6% (w/w) sodium salicylate plus 10% (w/w) dimethyl sulfoxide in white petrolatum USP ointments are shown in Figs. 1–6.

The results of the statistical t test (Tables I and II) indicate that percutaneous absorption of salicylic acid was increased significantly when sorbitan monopalmitate, sorbitan trioleate, poloxamer 231, poloxamer 182, polyoxyethylene 4 lauryl ether, polyoxyethylene 2 oleyl ether, and polyoxyl 8 stearate were each added to the ointment containing dimethyl sulfoxide and salicylic acid in white petrolatum USP. The percutaneous absorption of sodium salicylate was increased significantly when sorbitan monolaurate, sorbitan monopalmitate, and poloxamer 182 were each added to the ointment containing dimethyl sulfoxide and sodium salicylate in white petrolatum USP.

DISCUSSION

A statistical analysis of the results seems to indicate that some surfactants functioned as penetrant carriers, enhancing the percutaneous absorption of salicylic acid and sodium salicylate. When these surfactants were added to an ointment containing salicylic acid and dimethyl sulfoxide, percutaneous absorption of salicylic acid rapidly increased during the first 2 hr following ointment application.

Salicylic acid, which is lipid soluble, penetrates more readily through the skin than the nonlipid-soluble sodium salicylate (9). Substances that are lipid soluble penetrate the cell membrane because of their fat-soluble nature; on the other hand, the uptake of the water by the cell membrane protein provides entry for water-soluble substances (10).

The 10% (w/w) salicylic acid in the ointment was completely solubilized by the quantity of dimethyl sulfoxide and surfactant added to the ointment. Approximately one-third of the 11.6% (w/w) sodium salicylate, equivalent to 10% (w/w) salicylic acid, was solubilized in the amount of dimethyl sulfoxide and surfactant. Adding surfactants and dimethyl sulfoxide to the ointment containing 10% (w/w) salicylic acid in white petrolatum resulted in a significantly rapid increased absorption of the salicylic acid. This increase could possibly be attributed to the ability of dimethyl sulfoxide to solubilize salicylic acid and serve as a penetrant carrier for salicylic acid.

Mixed surfactants of varying HLB values resulted in a prolonged percutaneous absorption effect of both salicylic acid and sodium salicylate.

The mechanism by which percutaneous absorption of salicylic acid and sodium salicylate is increased by nonionic surfactants in the presence of dimethyl sulfoxide is unknown. However, Higuchi (6) suggested that the activity coefficient of the acid and salt plays a major role in percutaneous absorption. Salicylic acid and sodium salicylate, held firmly by the white petrolatum, form a drug–vehicle complex exhibiting a low activity coefficient. The rate of release from such drug–vehicle combinations is slow. When dimethyl sulfoxide and surfactants are added to the ointment containing 11.6% (w/w) sodium salicylate in white petrolatum or 10% (w/w) salicylic acid in white petrolatum, the rate of release of salicylic acid and sodium salicylate may be increased by forming high activity coefficient complexes such as surfactant–drug, dimethyl sulfoxide–drug, and dimethyl sulfoxide–surfactant–drug. Therefore, the percutaneous absorption of salicylic acid and sodium salicylate may be enhanced by these complexes.

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