Percutaneous Absorption of Salicylic Acid after Repeated (14-day) *In Vivo* Administration to Normal, Acnegenic or Aged Human Skin

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Abstract □ The objective of the present work was to determine the relative bioavailability of salicylic acid (SA) after repeated (14-day) topical application to subjects who presented normal, acnegenic, or photodamaged facial skin. To emulate exposure characteristics likely to be encountered by subjects in these two subpopulations, individuals presenting facial acne were treated with 2% SA in a hydroalcoholic vehicle, and volunteers with aged or photodamaged skin received a comparable topical dose of SA in a cream (moisturizer-like) vehicle. Plasma concentration–time profiles and cumulative urinary excretion of SA were measured after the last dose in subjects who had received 15 consecutive daily topical applications of 27 mg of SA or oral doses of 81 mg of acetylsalicylic acid (ASA). The rate and extent of percutaneous absorption of SA were not affected by facial skin condition. Faster rates of absorption (C_{max}) were obtained with a hydroalcoholic compared with a cream vehicle. Systemic SA exposures were at least five-fold higher with oral ASA than topical SA. Based on systemic salicylate concentrations resulting from ingestion of 81 mg of ASA, these results support that patients without gross skin disorders are at minimal risk of adverse systemic effects from routine use of topical products containing 2% SA.

Introduction

Salicylic acid (SA) is widely used as a topical therapeutic agent for a variety of skin diseases, including acne, psoriasis, and ichthyosis. As an over-the-counter (OTC) topical medication, SA is approved at concentrations up to 2% (w/w) by the FDA Final Acne Monograph.[1] Numerous studies have demonstrated that following deposition onto the skin, SA will penetrate the stratum corneum and enter the systemic circulation.[2–4] Topical application of 6% SA ointments to large body surface areas for the treatment of psoriasis and ichthyosis has been associated with high plasma concentrations of salicylates and even sporadic reports of clinical toxicities.[5,6] To our knowledge there have not been any reports associating topical use of 2% SA with these adverse systemic effects; however, as the number of products containing 2% SA increases in the marketplace, there is a need to better define cutaneous SA absorption from these preparations.

The primary objective of this study was to determine plasma salicylate levels in human subjects following application of 2% SA in two different vehicles as a function of facial skin condition. To this end, the study design allowed subject group designation to vary by both skin type and SA application vehicle. SA bioavailability from a hydroalcoholic vehicle was evaluated after topical application in subjects with normal facial skin and subjects with dermatologically confirmed mild to moderate facial acne. SA bioavailability from a cream vehicle was evaluated in subjects with normal facial skin and subjects with medically confirmed evidence of moderate to very severely aged and/or photodamaged facial skin. A fifth subject group that received 81 mg of aspirin (acetylsalicylic acid; ASA) daily rather than daily SA skin treatment was included as a reference control.

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Materials and Methods

Subjects—Thirty-eight female volunteers, 18 to 65 years of age, were assigned to four treatment groups based on dermatologically assessed facial skin characteristics: two groups of subjects presented normal skin, one group presented mild to moderate acne, a fourth group was selected for evidence of moderate to severely aged or photodamaged skin, and a fifth group, which served as the reference control, was required to meet no facial skin criteria. Overall, no subjects in the five treatment groups had active skin disease, scarring, or excessive hair formation. Furthermore, for normal skin designation, subjects had no apparent acne and an aged or photodamaged designation of mild or less. For aged or photodamaged designation, subjects had no apparent acne, and presented with at least moderate facial wrinkling, and/or uneven texture or tone (color). The degree of photodamage was assessed with a photographic comparison scale that allowed the investigator to select 1 of 6 designations from mild to extremely severe. The investigator who performed these assessments had been previously familiarized with this scale, which is similar to that used by Bhawan et al.[7] For acne group designation, an overall acne grade of 3 - 9 according to the global acne scale, combined with a full facial lesion count of at least 15 open or closed non-inflamed comedones and at least 15 inflamed papules and/or pustules was required. The global scale used was modified from Burke and Cunliffe.[8]

Only female subjects were included in the study because some of the more concerning toxicological effects of salicylates are in the areas of maternal reproductive and fetal toxicity. All subjects were determined to be in good health by general medical and clinical chemistry evaluations, which included blood chemistry, routine hematology and serology, urinalysis, urine pregnancy test, and drug screen. Subjects selected were not on any OTC medications, prescription drugs, or oral contraceptives and were either surgically sterile, postmenopausal, or using an acceptable barrier method of contraception.

Subjects were instructed to avoid salicylates in oral and topical medications, as well as other potential sources of salicylates (e.g., wintergreen oil) for at least 1 week prior to the start of the study and throughout the duration of the study. Only nonsmokers and subjects without a history of drug and alcohol abuse were included in the study. Subjects were also instructed to refrain from the intake of alcohol or caffeine during the study and for at least 72 h prior to study start.

Study Design—This study received institutional review board approval, and written informed consent was obtained from each volunteer prior to her entering the study. The study was designed to evaluate serum salicylate concentration–time profiles in female subjects after topical application of 2% SA. SA was applied in either a cream or hydroalcoholic liquid to the subjects' face and neck. Serum salicylate concentration–time profiles also were compared with female subjects who received oral administration of acetylsalicylic acid (ASA). Subjects were divided into five groups of 9 to 10 individuals; four groups were based on skin type (aged, acnegenic, and two normal groups) as already defined, and one group was based on administration route (oral).

Subjects who received topical SA were designated by both skin type and application vehicle. Nineteen subjects with normal skin (normal skin subjects) were enrolled in the study. Ten of these subjects were

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treated with the 2% SA cream. The remaining nine normal skin subjects were treated with the 2% SA hydroalcoholic liquid. Nine subjects with aged (photodamaged) skin (aged skin subjects) were enrolled in the study and treated with the 2% SA cream and nine subjects with acne (acne skin subjects) were treated with the hydroalcoholic liquid. All facial applications of SA were performed once daily at the study site for 16 days by trained study personnel. This treatment interval was selected on the basis of known skin cell cycle dynamics to allow for the expression of any potential application-related effects on skin barrier function that could possibly impact SA percutaneous absorption.[9] The amount of test material applied was ~1.25–1.50 g (25–30 mg SA), and the material was applied to the face and neck only. Subjects in the oral aspirin reference group came to the clinical site daily to receive 81 mg of ASA with 8 ounces of water once daily. On day 15 of the study, all subjects were confined to the testing facility for 24 h. Blood samples were taken periodically for pharmacokinetic analyses. Total urine was collected to determine salicylate excretion.

Test Materials—Two different SA application vehicles were included in this study: a hydroalcoholic liquid containing 63% water, 35% ethanol, and 2% salicylic acid; and a cream consisting of 80% water, 2% salicylic acid, and 18% cosmetic excipient mixture (PPG-14 butyl ether, glycerin, cetyl and stearyl alcohols, polyquaternium 37, mineral oil, dimethicone, Steareth-21, cyclomethicone, and triethanolamine). Bayer Children's Aspirin (lot #KD340) was purchased commercially (81 mg of ASA per tablet).

Blood and Urine Sample Collection—Blood samples (7 mL in EDTA/Na fluoride vacutainers) were obtained by venipuncture of the forearm on study days 0, 7, and 12. All subjects were sequestered at the clinical site for a 24-h period on study day 15 and provided with three controlled meals throughout the day. Upon arrival to the facility, each subject was instrumented with an indwelling forearm venous catheter to obtain a pre-dose blood sample, as well as post-dose samples at 5, 15, 30, and 45 min, and 1, 2, 3, 4, 6, 8, 10, 12, 16, and 24 h. After collection, the samples were centrifuged at 3000 rpm for 10 min, and plasma was frozen at −70 °C until assayed for salicylate content. For each subject, urine was collected and kept under refrigeration throughout the collection period. At the completion of the 24-h collection period, each urine sample was weighed and an aliquot was maintained frozen at −70 °C until assayed for salicylate content.

Analysis of Salicylate in Blood and Urine—ASA(plasma), SA (plasma), and total salicylate concentrations (urine) were determined by high-pressure liquid chromatography (HPLC) with a procedure modified from Buskin et al.[10] and Siebert and Bochner.[11] For the urine assay, the sample (one part urine) was first diluted in a 1:1.5 parts water:concentrated hydrochloric acid mixture and hydrolyzed by autoclaving at 120 °C for 60 min to convert salicylate metabolites (mainly salicyluric acid) to SA. The urine sample prepared in this manner was then subjected to the same analysis routine as used for plasma ASA and SA, which involved acidification, extraction from plasma with ether/hexane, back extraction with phosphate buffer, and determination by HPLC. Tandem UV and fluorescence detection allowed simultaneous determination of ASA and SA. ASA was determined with a KontroN 432 UV detector (absorption at 234 mm), and SA was determined by fluorescence with a Hitachi F 1080 (excitation, 300 nm; emission, 433 nm). The ASA method quantification limit was 20 μg/L, and the SA quantification limit was 5 μg/L. Standard curves were linear over ranges of 20 to 1000 and 5−1000 μg/L, respectively, for ASA and SA. Percent recovery for plasma SA, as determined with samples spiked with SA at 200 μg/L, was 97 ± 6% (mean ± standard deviation; $n = 17$). For urinary SA, percent recoveries of samples spiked with 1:1 mixtures of SA:salicyluric acid ($n = 8$–10) were 88 ± 8% (100 μg/L), 88 ± 2% (200 μg/L), and 84 ± 1% (500 μg/L).

Data Evaluation and Statistical Analysis—The maximum plasma concentration (C_{max}) of SA and the time at which the maximum concentration occurred (T_{max}) were determined from the individual SA plasma concentration−time profiles. The terminal exponential half-life ($t_{1/2,z}$) was estimated from linear least-squares regression of the terminal phase of the log concentration−time profile following the last dose. Area under the plasma concentration−timecurve (AUC) was determined by the linear trapezoidal rule.[12,13]

To determine the time to reach steady-state, trough plasma SA concentrations at days 7, 12, 15, and 16 were analyzed by one-way repeated measures analysis of variance (ANOVA), which included factors for skin type (normal, acnegenic, aged). The treatment by skin type interaction term was included to test for differential effects over time as a function of skin type. Pharmacokinetic parameters (C_{max}, T_{max}, $t_{1/2,z}$, and AUC) were analyzed by one-way independent measures ANOVA. As appropriate, all *post hoc* pairwise comparisons were done by the Student-Newman-Keuls multiple comparison procedure.[14]

To calculate the relative bioavailability (F_{rel}) of SA following topical administration versus oral administration, the following equation was used: F_{rel} (%) = [AUC (topical)]/[AUC (oral)] × [dose (oral)]/[dose-(topical)].

Table 1—Demographic Data for Study Participants[a]

Skin Type	Age, Years (Range)	Weight, kg (Range)	Height, cm (Range)
Normal skin /hydro-alcoholic vehicle ($n = 10$)	29.4 ± 7.62 (19–42)	62.5 ± 10.3 (50–76.4)	160.9 ± 7.71 (149.9–172.3)
Normal skin/cream vehicle ($n = 10$)	34.3 ± 10.3 (19–44)	65.6 ± 10.0 (50–79.5)	162.3 ± 7.49 (150–172.7)
Acnegenic ($n = 9$)	28.4 ± 5.4 (22–38)	68.0 ± 12.2 (50.5–86.8)	169.1 ± 10.6 (150–186)
Aged ($n = 10$)	52.0 ± 7.9 (38–62)	65.9 ± 9.3 (45.9–76.4)	162.1 ± 6.2 (152–170)
N/A[c] ($n = 10$)	38.1 ± 7.9 (24–47)	68.8 ± 12.3 (48.5–93.0)	162.6 ± 5.9 (152–170)

[a] Subject demographics were determined at study enrollment. As described in *Results*, three of the subjects included in Table 1 were dropped from data analysis. Data presented are mean ± SD. The range for each observation is given in parenthesis. [b] Race was ~20% black and 80% Caucasian for normal skin and oral ASA groups and 100% Caucasian for acnegenic and aged skin groups. [c] N/A, Not applicable. These subjects were assigned to receive oral ASA and therefore were not required to meet a facial skin criterion.

Results

Subject demographics are presented in Table 1. There were no statistical differences in the weight and height variations between the treatment groups. Subjects classified with aged or photodamaged skin (average age of group was 51 years) were significantly older than either of the two groups presenting normal skin or the subjects with acne.

All but one subject completed the study. Subject 10 was dropped because of failure to return to the study site for daily administration of test material. A second subject (subject 30) was excluded from data analysis because of abnormally high baseline levels of salicylates on study day 0, suggesting noncompliance with the self-medication requirements for the study. Subject 45 was also excluded from data analysis because of abnormally high baseline concentrations of SA on study day 15, suggesting similar noncompliance. There was no clinically observed skin irritation as a result of test material application in any of the study subjects, nor did subjects receiving oral aspirin report any adverse reactions. The average SA dose administered on day 15 of the study for the topically treated subject groups was 27 ± 0.8 mg. Importantly, there were no differences in the total amount of SA applied to the skin between topical treatment groups. Because topical preparations were applied daily by the same trained personnel, we would anticipate that daily doses across the study were at or about 27 mg.

Prior to administration of topical or oral salicylate, trough blood samples were collected on study days 7, 12, 15, and 16 to determine steady-state levels (Table 2). These results indicate that steady state was reached by day 7.

The plasma concentration−time profiles for SA after topical administration on the 15th day are illustrated in Figure 1. The corresponding pharmacokinetic parameters are shown in Table 3. Both the SA plasma concentration−time profiles and extent of percutaneous absorption of SA were influenced by the vehicle. Peak plasma SA concentrations were significantly

Table 2—Trough Plasma Salicylate Concentrations in Subjects Treated Daily with Topical or Oral SA[a]

Facial Skin	Vehicle	Plasma Salicylate Levels (μg/L) Day 7	Day 12	Day 15	Day 16
Normal	Cream	36.10 ± 21.29[a]	14.40 ± 2.23	23.70 ± 8.06	29.50 ± 6.99
Normal	Hydroalcohol	52.11 ± 13.08	44.00 ± 8.27	40.33 ± 7.86	41.67 ± 6.47
Aged	Cream	36.44 ± 5.64	38.11 ± 9.89	29.33 ± 11.63	21.56 ± 4.87
Acnegenic	Hydroalcohol	60.78 ± 21.29	43.56 ± 13.08	35.56 ± 9.93	34.56 ± 6.43
N/A	Oral aspirin[b]	<10.0[c]	<5.0	<10.0	<10.0

[a] Data presented are the mean ± SEM of $n = 10$ subjects in the normal/cream group and $n = 9$ in the remaining groups. [b] N/A, Not Applicable. Subjects scheduled for oral ASA administration were not required to meet a facial skin criterion. [c] All subjects had concentrations less than level indicated, and most had nondetectable concentrations.

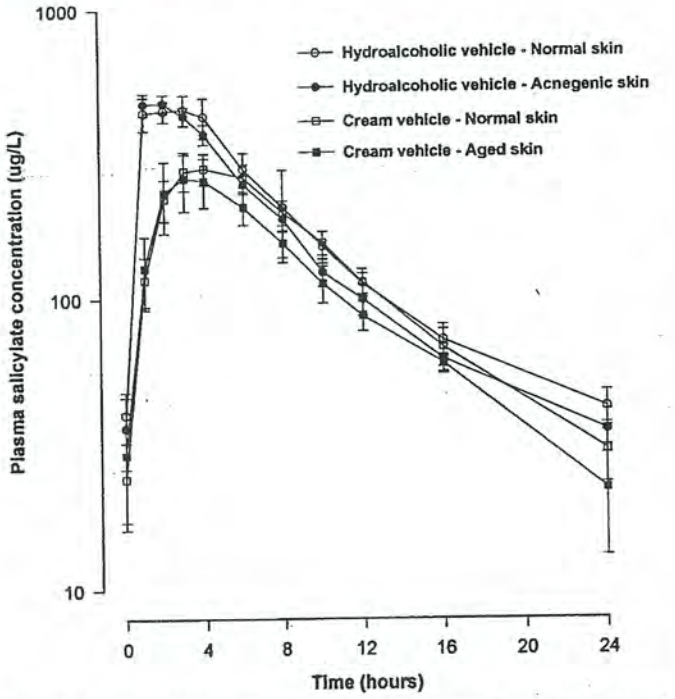

Figure 1—Plasma concentration–time profiles of SA in subjects presenting normal, aged, and acnegenic facial skin, after topical (face/neck) administration of a hydroalcoholic or cream vehicle containing 2% (w/v) SA. The data presented are the mean ± SEM for $n = 10$ (normal/cream group) or $n = 9$ (all other groups). Where not shown, the SEM bar was contained within the corresponding symbol. For clarity, plasma SA levels measured at time points between 0 and 1 h are not shown in the figure.

higher and time to peak occurred earlier in subject groups that received 2% SA in hydroalcoholic vehicle as compared with 2% SA in the cream vehicle. There was a statistically significant effect of treatment on salicylate terminal exponential half-life as determined by one-way analysis of variance ($F_{4,46} = 6.57$; $p < 0.0003$). The SA terminal exponential half-life among subjects receiving oral ASA was significantly shorter than that observed in each of the topical treatment groups ($p < 0.05$). No significant pairwise differences in the terminal exponential half-life was seen among any of the groups treated with topical SA (i.e., no significant skin or vehicle effects by pairwise comparisons). AUC SA values were significantly higher in hydroalcoholic SA-treated subjects than in the cream-treated counterparts (Table 3). Skin type did not significantly influence any of the kinetic parameters examined.

The SA plasma concentration–time profile for subjects who received 81 mg of ASA is provided in Figure 2. For the subjects in this treatment group, the average time to peak plasma concentration was 0.71 h, with the average peak plasma SA concentration being 5282 μg/L. The corresponding plasma AUC value for this group was 22 010 μg h/L. Plasma concentrations of the parent compound, ASA, were also measured in this study (data not given). Peak ASA levels were achieved ~30 min after oral administration and then declined rapidly with no detectable ASA in the plasma at 3 h post-administration. Peak concentrations of ASA (30 min) ranged from 80 to 300 μg/L. Peak and AUC concentrations of SA were significantly greater (5- to 10-fold) for the oral ASA group than the subjects receiving SA via topical administration.

Cumulative 24-h urinary SA excretion is shown in Table 4. No statistically significant pairwise differences in cumulative urinary levels of SA were seen among any of the groups treated with topical SA (i.e., no significant skin or vehicle effects by pairwise comparisons). Urinary recovery was significantly higher ($p < 0.05$) in the oral ASA group compared with each of the topical SA treatment groups.

Discussion

In general, SA is considered to penetrate well across human and animal skin.[3,4,15,16] However, percutaneous absorption of SA is influenced to a significant extent by variables such as concentration, type of vehicle used for solubilization, skin hydration, and barrier condition.[2–4] As a result, estimating systemic exposure to SA from use of commercial 2% SA skin care products is difficult given the existing literature. This study design allowed for quantification of the relative SA dermal absorption from two skin application vehicles (hydroalcoholic liquid and cream). Acnegenic skin subjects were treated with the hydroalcoholic vehicle because SA acne products often utilize alcohol-based matrices, and photodamaged or aged skin subjects were treated with the cream vehicle because cosmetic products containing SA most often utilize cream-based matrices.

Penetration of SA across the skin occurred readily following its application in either the hydroalcoholic liquid or the cream. However, the nature of the vehicle influenced both the rate and extent of absorption, with the hydroalcoholic vehicle allowing for higher percutaneous absorption. Although a comparative finding such as this has not previously been reported, prior studies have demonstrated significant percutaneous absorption of SA from alcohol based vehicles.[17–19] Interestingly, in our studies, the SA plasma concentration–time profile did not differ significantly between the acnegenic and the normal skin subjects or between photodamaged/aged and normal skin subjects, indicating that skin type did not influence the rate or extent of SA absorption. Previous studies with abraded animal skin and diseased human skin demonstrated that SA absorption was significantly greater through compromised skin, regardless of skin delivery vehicle.[3,15,20] For example, in a study by Taylor and Halprin,[4] the average topical absorption from a 6% SA cream was ~70–80% of the applied dose in psoriatic patients. Relative to those reports,

Table 3—Steady-State SA Pharmacokinetic Parameters in Subjects Presenting Normal, Aged or Acnegenic Facial Skin after Topical Application of 2% SA or in Subjects Receiving One Daily Oral Dose of 81 mg ASA[a]

Skin Type	Vehicle	Peak Plasma Salicylate Levels (μg/L)	Time to Peak Plasma Salicylate Levels (h)	Terminal Exponential Half-Life Plasma Salicylate (h)	Area under the Curve Plasma Salicylate Levels (μg h/L)
Normal	Cream	293 ± 37	4.30 ± 0.40	5.83 ± 0.73	3108 ± 293
Aged	Cream	275 ± 58	4.11 ± 0.58	5.93 ± 0.83	2636 ± 302
Normal	Hydroalcohol	525 ± 66[b]	1.89 ± 0.35[b]	7.62 ± 0.82	4225 ± 425[b]
Acnegenic	Hydroalcohol	487 ± 41	1.67 ± 0.24	8.06 ± 1.12	3893 ± 329
N/A	Oral ASA[c]	5282 ± 457[d]	0.71 ± 0.25[d]	2.62 ± 0.46[d]	22010 ± 3907[d]

[a] Data presented are the mean ± SEM for $n = 10$ (normal/cream group) or $n = 9$ (all other groups). [b] Significantly different from subjects presenting normal facial skin treated with 2% SA in a cream vehicle ($p < 0.05$). Significant differences were not found within vehicle type in subjects presenting normal compared with aged or acnegenic facial skin. [c] N/A, Not applicable. Subjects scheduled for oral ASA treatment were not required to meet facial skin criteria. [d] Statistically different from all topical treatments.

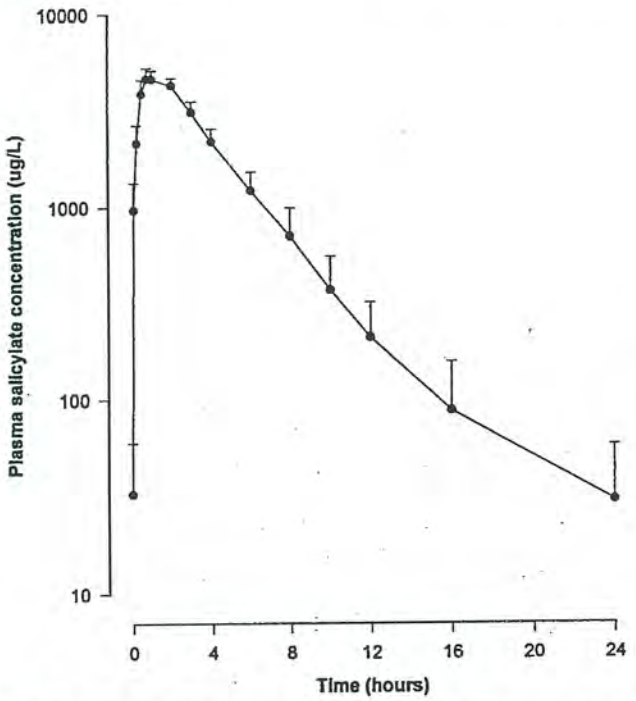

Figure 2—Plasma concentration–time profile of SA in subjects receiving oral administration of 81 mg of ASA. The data presented are the mean ± SEM for $n = 9$ subjects at eachtime point. (Note the 10-fold change in the y axis compared with Figure 1.)

Table 4—24-Hour Cumulative Urinary SA Excretion in Subjects Treated Topically with 2% SA or Orally with 81 mg of ASA[a]

Skin Type	Vehicle	Total 24-Hour Cumulative Urinary Salicylate Excretion (mg)
Normal	Cream	6.10 ± 1.01
Aged	Cream	6.44 ± 0.94
Normal	Hydroalcohol	5.56 ± 0.69
Acnegenic	Hydroalcohol	8.00 ± 0.67
N/A[b]	Oral ASA	37.56 ± 4.02[c]

[a] Data presented are the mean ± SEM for $n = 10$ (normal/cream group) or $n = 9$ (all other groups). [b] N/A, Not applicable. Subjects scheduled for oral aspirin treatment were not required to meet facial skin criteria. [c] Statistically different from all topical treatments.

the present data indicate that neither of the skin types we evaluated constitute a compromised barrier for SA absorption.

In the present study, bioavailabilities for topically applied SA among normal skin type subjects were 57.6 and 44.0% for the hydroalcoholic and cream delivery vehicles, respectively. The lower absorption of topically compared with orally administered salicylates observed in this study is in agreement with earlier reports by other investigators.[3,4,21] Moreover, the slower half-life observed after topical compared with oral administration indicated that absorption is the rate-limiting step for absorption of topically applied SA.

This study has provided new data on the percutaneous absorption of SA from hydroalcoholic and cream vehicles and on the impact of different skin types on bioavailability of the compound. This pharmacokinetic information allows for improved estimates of systemic SA contributions from topically applied products. Based upon the outcome of this study, systemic exposures to SA from the use of topical 2% SA products are ~15% of those obtained following oral administration of 81 mg of ASA and substantially below those associated with adverse SA-related effects.

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