

Biophysical characterization of skin damage and recovery after exposure to different surfactants

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The majority of adverse skin reactions to personal-care products are presumed to be caused by irritant substances, like surfactants. In this study, different aspects of the irritant reaction after a single exposure to 8 surfactants were characterized during 2 weeks. Solutions of 2% sodium lauryl sulfate, 5% sodium C12–15 pareth sulfate, 5% sodium cocoyl isethionate, 10% disodium laureth sulfosuccinate, 10% sodium cocoamphoacetate, 10% cocamide DEA, 10% cocamidopropyl betaine and 10% lauryl glucoside, respectively, were applied to the forearm of 12 volunteers. Clinical assessment, an evaporimeter, a laser Doppler flowmeter and a corneometer were used for evaluation. The surfactants induced different degrees of irritation. Erythema, transepidermal water loss and skin blood flow exhibited a similar time course, which seemed to be inversely related to the delayed scaling and reduced skin capacitance. The mechanism of the damaging effect of the surfactants seems to be similar, although some minor differences were noted.

Key words: surfactants; irritant contact dermatitis; bioengineering methods; barrier function; recovery time. © Munksgaard, 1999.

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The use of toiletries such as cleansers, soaps and shampoos may cause adverse effects (1, 2) like skin irritation, dryness and itching. This skin irritation potential may vary between products of different brands (3, 4), probably due to their composition of surfactants.

Surfactants may damage the skin barrier by several mechanisms. Direct and indirect damaging effects have been proposed, such as interaction with keratin (5), changes in lipid structure (6), and inflammatory processes (7) with keratinocyte-derived cytokine release (8). However, there are few comparative studies of the irritation potential of different surfactants, and the skin barrier recovery after exposure to individual surfactants with different ionic and structural properties is an area not well explored (9, 10).

The objectives of this study were to examine and compare irritant reactions induced by commonly used surfactants, with special attention to barrier recovery in order also to detect delayed effects. A 48-h patch test was chosen to enhance the inherent toxic properties of the surfactants. The degree of irritation was assessed clinically and transepidermal water loss (TEWL), skin surface blood flow

and skin capacitance values were measured objectively during 14 days. Sodium lauryl sulfate (SLS) was among the surfactants included, since it is known as a model irritant in dermatological research (11). To our knowledge, this is the 1st study comparing skin barrier recovery after exposure to anionic, nonionic and amphoteric surfactants.

Materials and Methods

Study population

12 healthy volunteers between 22 and 64 years of age (2 male) participated in the study after having given their written informed consent. The study was approved by the local ethical committee.

Chemicals

The following surfactants were used:

Anionic. Sodium C12–15 pareth sulfate (PAR), molecular weight (MW) 417 g/mol, (Elfan NS 252, Akzo Nobel, Amersfoort, The Netherlands), sodium lauryl sulfate (SLS) MW 310 g/mol, (Texapon ZHC, Henkel, Düsseldorf, Germany), sodium cocoyl isethionate (ISE) MW 337 g/mol, (El-

fan AT 84, Akzo Nobel, Amersfoort, Netherlands), disodium laureth sulfosuccinate (SUL) MW 552 g/mol, (Surfagene S30, Chemische fabrik Chem-Y GmbH, Germany).

Nonionic. Lauryl glucoside (LAU) MW 420 g/mol, (Plantaren, Henkel, Düsseldorf, Germany), cocamide DEA (DEA) MW 310 g/mol, (Comperlan KD, Henkel, Düsseldorf, Germany).

Amphoteric. Sodium cocoamphoacetate (AMP) MW 365 g/mol, (Miranol Ultra, Rhône-Poulenc, Cranbury, N.J., USA), cocamidopropyl betaine (BET) MW 350 g/mol, (Tego Betain F50, Th. Goldschmidt AG, Essen, Germany).

The surfactants were supplied in different concentrations and pH. They were diluted in a citrate buffer to a citrate concentration of 5 mM, and a pH of 6 ± 0.5 . In the study, the surfactant concentrations were as follows (molar concentrations in parenthesis): 10%: DEA (323 mM), BET (286 mM), AMP (274 mM), LAU (238 mM), SUL (181 mM); 5%: ISE (148 mM), PAR (120 mM); 2% SLS (65 mM). The concentrations were based on literature data (11–14) and chosen after initial results from a pilot study (data not included in the present study), where all surfactants were applied in 5% solutions (molar concentration range 91–161 mM). The aim was to induce a certain skin damage in the acute phase, and therefore the concentrations were adjusted in the present study, with increased concentrations to 10% for the nonionic and amphoteric surfactants and also the anionic SUL. The concentration of SLS was lowered to 2%. Citrate buffer (10 mM) served as control.

Procedure

50 μ l of each surfactant solution was pipetted into large aluminium chambers (12 mm Finn Chambers, Epitest Oy, Finland) containing 1 layer of filter paper. The chambers were attached to the left volar forearm skin with adhesive tape (Scanpore, Norgeplaster A/S, Oslo, Norway). After 48 h the patches were removed. The application sites were randomized using a Latin square, thus avoiding treatment site effects.

Each site was examined by the same investigator 1 h after patch removal (day (D) 1) and after 24 h (D 2), on D 5, 9 and 14. The readings at D 14 were allowed to vary ± 1 D and still be labeled 14. Erythema and scaling were graded separately using the method of Frosch and Kligman (3), as is shown in Table 1. After the clinical evaluation non-invasive measurements were made.

TEWL was measured with an evaporimeter (Evaporimeter EP2, Servomed, Stockholm, Sweden) (15). The output was recorded by a computer, and the recording was made for 40 s after a

Table 1. Irritancy scale (3)

	Scale
erythema	1 (slight redness, spotty or diffuse) 2 (moderate, uniform redness) 3 (intense redness) 4 (fiery red with oedema)
scaling	1 (fine) 2 (moderate) 3 (severe with large flakes)

stabilization period of 30 s. Probe protection cover with a screen and grid was used.

The microvascular blood flow was measured with a laser Doppler flowmeter (Periflux Laser Doppler Flowmeter, Perimed, Sweden) (16), and the results were registered on a printer (Servogor 120 BBC). The instrument was equipped with a special multi-fiber probe (PF 113 Integrating probe, Perimed) which has 7 fiber triplets, 1 in the middle and 6 around it, forming a circle 8 mm in diameter, in the probe head. This means 7 spots instead of 1 are being recorded, which reduces variation due to spotty erythema.

Capacitance as a parameter for stratum corneum (SC) hydration was measured with a corneometer (Courage & Khazaka, Cologne, Germany). Because water has by far the highest dielectric constant in the skin, a change in water content is suggested to change the displayed value of the capacitance (arbitrary units) in the corneometer (17).

All measurements were carried out in a draught-free room at a temperature of $23 \pm 1^\circ\text{C}$ and a relative humidity of $18 \pm 6\%$. The study was accomplished during November-January.

Statistics

To test the hypothesis that there was no difference in the effect of the individual surfactants compared to control, with respect to the 3 variables TEWL, skin blood flow and capacitance, the non-parametric 1-sample Wilcoxon test median method was used. Also, 1-sample Wilcoxon confidence intervals on the differences between control and each surfactant were calculated. The software used was Minitab® (Minitab Inc, State College, PA, USA). Correction for multiplicity was made according to Holm (18) to get the overall significance level of $p < 0.05$.

Results

Clinical examination (Table 2 & 3)

On D 1, erythema was present in sites exposed to the surfactants and the control. The most pronounced erythema was found after exposure to

Table 2. Scoring of visual erythema (% of total) after exposure to 8 surfactants and control ($n=12$) on D 1–14; the patches were removed on D 1

Time (days)	Treatment								
	control	SLS	ISE	PAR	SUL	AMP	BET	DEA	LAU
1	17	58	42	35	13	33	23	25	21
2	2	52	31	38	10	21	21	21	13
5	2	42	23	19	4	10	4	6	6
9	0	27	13	8	0	0	2	4	2
14	0	17	10	8	0	4	4	2	2

Table 3. Visual scoring of scaling (% of total) after exposure to 8 surfactants and control ($n=12$) on D 1–14; the patches were removed on D 1

Time (days)	Treatment								
	control	SLS	ISE	PAR	SUL	AMP	BET	DEA	LAU
1	6	0	0	0	0	0	0	0	0
2	0	0	3	0	0	3	3	0	3
5	0	47	36	36	11	22	22	14	8
9	6	39	36	31	6	22	17	19	8
14	3	14	22	22	8	14	11	11	6

SLS. During the next 2 weeks, the erythema decreased, but slight erythema was still present in several sites on D 14. After a few days scaling developed and reached a maximum after about 1 week. Scaling still existed on D 14, especially in the sites exposed to ISE and PAR.

Instrumental examination

On D 1 and 5 after exposure, TEWL was elevated for most of the surfactants studied, and on D 2 for all surfactants (Fig. 1, Table 4). TEWL remained elevated after exposure to PAR for at least 2 weeks, and after SLS for at least 9 days. Cutaneous blood flow was elevated for SLS, ISE, PAR and AMP on D 2, and also for SLS on D 1 and 9 (Fig. 2, Table

4). The blood flow decreased and reached baseline for all treatments within 2 weeks. There was no significant increase in the blood flow at any time point after exposure to the nonionics, BET or SUL.

Immediately after SLS, the capacitance was increased, while the opposite was true after exposure to SUL, BET, DEA and LAU (Fig. 3, Table 4). On D 5, the capacitance was below normal for all surfactants except SUL, which was not significantly different from control after the 2nd day. The capacitance was still reduced 9 days after exposure to all surfactants but SUL and LAU. After 2 weeks, the capacitance was still below normal after SLS and AMP.

Discussion

Surfactant-induced skin irritation is a multifaceted phenomenon with several underlying mechanisms. In order to monitor different aspects of the irritant reaction following a single occlusive application of different surfactants, non-invasive bio-engineering methods were used. TEWL was determined, since the subclinical response of an increased TEWL is a sensitive measure of barrier damage (19, 20). The cutaneous blood flow was measured as a component of the inflammatory response (7). Moreover, skin capacitance was followed, as it is supposed to reflect skin hydration (17) and has been reported to correlate with the clinical appearance of scaling (9, 21).

The results in the present study are consistent with the general view that surfactants differ in irritation potential. This is not only a concentration

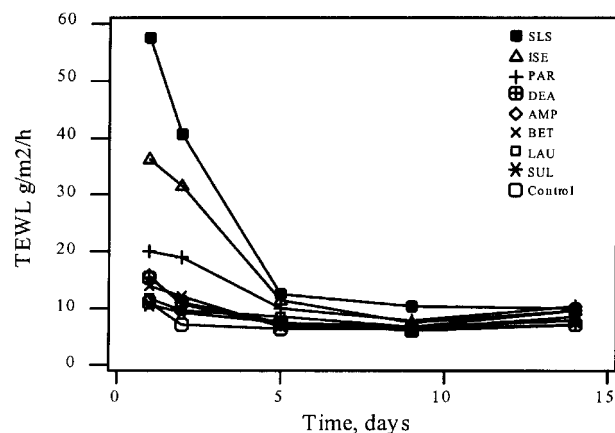


Fig. 1. Time course of transepidermal water loss (TEWL, $\text{g/m}^2/\text{h}$) of surfactant-treated sites and control. Median values are shown ($n=12$).

Table 4. Statistical comparison (1-sample Wilcoxon test median) and 1-sample Wilcoxon confidence intervals (C.I.) of the differences between the effect of the control and the effect of the surfactants. In order to get an overall significance level of $p < 0.05$, the individual significance level (p) of each comparison is corrected (p^*), depending on the multiplicity, according to Holm (18)

Treatment	TEWL C.I.	p	p^*	Bloodflow C.I.	p	p^*	Capacitance C.I.	p	p^*
D 1									
SLS	26.8, 54.7	0.003	0.018	11.5, 57.5	0.005	0.04	5.5, 21.0	0.003	0.021
ISE	15.2, 32.2	0.003	0.015	2.0, 30.5	0.034	NS	1.0, 10.0	0.045	NS
PAR	4.4, 17.3	0.003	0.024	3.0, 39.5	0.025	NS	-9.0, 0.5	0.071	NS
SUL	-1.4, 4.3	0.182	NS	-6.5, 13.5	0.814	NS	-11.0, -3.5	0.006	0.024
AMP	4.5, 8.8	0.003	0.021	2.0, 24.5	0.033	NS	-10.0, 2.5	0.583	NS
BET	1.1, 8.7	0.017	NS	-4.0, 36.5	0.308	NS	-13.5, -5.0	0.003	0.024
DEA	1.6, 9.6	0.011	0.044	-3.5, 26.0	0.108	NS	-14.0, -6.5	0.003	0.018
LAU	-0.9, 5.1	0.147	NS	-14.0, 26.5	0.456	NS	-12.5, -5.0	0.005	0.025
D 2									
SLS	21.0, 39.9	0.003	0.018	32.0, 63.0	0.003	0.024	-11.5, 8.0	0.965	NS
ISE	14.4, 26.9	0.003	0.012	20.0, 47.0	0.003	0.021	-9.0, 6.5	0.666	NS
PAR	6.4, 16.3	0.003	0.024	12.0, 41.0	0.005	0.025	-8.0, 2.5	0.224	NS
SUL	0.9, 5.6	0.015	0.015	-1.5, 11.5	0.126	NS	-4.0, 4.0	0.894	NS
AMP	2.1, 5.5	0.004	0.012	7.0, 22.0	0.004	0.024	-11.5, 0.5	0.100	NS
BET	2.4, 7.4	0.003	0.021	1.0, 22.0	0.034	NS	-12.5, -3.5	0.013	NS
DEA	2.5, 7.7	0.003	0.015	2.0, 17.0	0.041	NS	-12.5, -2.5	0.004	0.032
LAU	1.3, 5.2	0.007	0.014	-0.5, 11.0	0.078	NS	-11.0, -1.5	0.028	NS
D 5									
SLS	3.1, 15.4	0.003	0.018	3.0, 24.0	0.01	NS	-39.5, -19.0	0.003	0.021
ISE	3.0, 7.1	0.003	0.015	-0.5, 8.0	0.110	NS	-24.5, -10.0	0.003	0.018
PAR	2.2, 4.8	0.003	0.024	0.0, 8.0	0.044	NS	-18.5, -9.5	0.003	0.024
SUL	0.9, 2.9	0.009	0.036	-1.5, 2.0	0.534	NS	-8.0, 2.0	0.241	NS
AMP	0.7, 2.4	0.011	0.033	-1.0, 3.5	0.262	NS	-11.5, -5.5	0.004	0.02
BET	0.2, 1.8	0.053	NS	-1.0, 3.5	0.286	NS	-17.0, -4.5	0.009	0.027
DEA	-0.3, 1.9	0.158	NS	-0.5, 1.5	0.359	NS	-14.5, -8.0	0.004	0.016
LAU	1.0, 2.4	0.003	0.021	-1.0, 6.5	0.689	NS	-11.5, -2.0	0.014	0.028
D 9									
SLS	2.5, 5.5	0.003	0.024	2.5, 10.0	0.004	0.032	-25.0, -7.0	0.005	0.035
ISE	1.0, 3.7	0.011	NS	0.5, 3.0	0.022	NS	-21.0, -7.5	0.006	0.036
PAR	0.9, 2.9	0.005	0.035	0.5, 4.5	0.025	NS	-20.5, -6.5	0.007	0.035
SUL	0.0, 2.2	0.068	NS	-1.0, 1.0	0.813	NS	-8.5, 2.5	0.308	NS
AMP	0.2, 2.5	0.028	NS	0.0, 2.5	0.083	NS	-10.0, -1.5	0.011	0.044
BET	0.2, 2.1	0.018	NS	0.5, 3.5	0.026	NS	-14.0, -3.0	0.013	0.039
DEA	-0.4, 1.3	0.248	NS	0.0, 2.0	0.029	NS	-12.5, -4.5	0.003	0.024
LAU	-0.2, 1.7	0.117	NS	-0.5, 3.0	0.083	NS	-10.0, -0.5	0.038	NS
D 14									
SLS	0.8, 2.8	0.013	NS	-1.5, 1.5	1	NS	-12.0, -2.5	0.004	0.032
ISE	0.4, 2.5	0.019	NS	-1.0, 2.0	0.61	NS	-10.5, 0.5	0.065	NS
PAR	0.6, 3.1	0.005	0.035	-1.0, 2.0	0.445	NS	-8.5, 0.5	0.083	NS
SUL	-0.1, 1.8	0.114	NS	-1.0, 1.5	0.594	NS	-5.0, 2.0	0.272	NS
AMP	0.3, 2.8	0.028	NS	-1.0, 3.0	0.327	NS	-8.5, -2.0	0.007	0.049
BET	0.6, 1.8	0.003	0.024	-2.0, 1.0	0.554	NS	-7.0, 2.0	0.23	NS
DEA	-0.5, 0.8	0.784	NS	-1.5, 1.0	0.767	NS	-5.5, 0.0	0.074	NS
LAU	-0.9, 1.3	0.563	NS	-1.0, 1.5	0.594	NS	-5.0, 0.5	0.17	NS

effect; illustrated for example by the fact that DEA was applied at a concentration $5\times$ higher than SLS but induced less irritation. Also in previous studies, SLS has been found to be more irritant than DEA (12), as well as ISE and SUL at equimolar concentrations (13, 14). A similar ranking of SLS, PAR, ISE and BET as in the present study, has been reported using excised stratum corneum for corneorosurfametry (22). However, in contrast to our findings, SUL and BET were found to cause higher TEWL than DEA in a repeated application test on humans (14).

The reason for the differences in irritancy between surfactants are not known, but the structure and ionic properties of the molecules may be important. For instance, it has been shown that substances with a carbon chain length of 12 have more pronounced biological effects than other carbon chain lengths (23–25). Moreover, increasing the ethylene oxide content of the molecule, which gives a larger hydrophilic part, appears to induce a corresponding decrease in irritation (22, 26, 27). In the present study, SLS (2%) induced the most irritation, followed by 2 other anionic surfactants, ISE

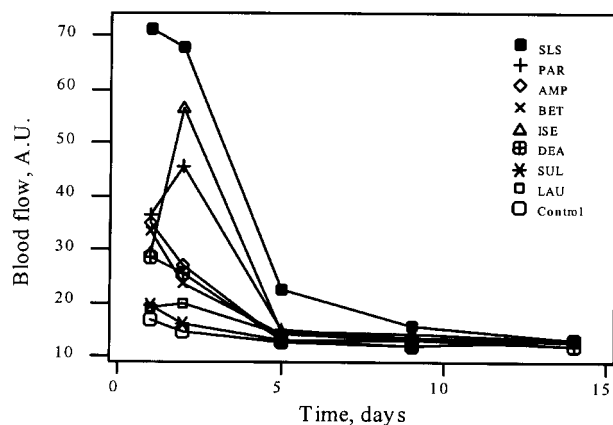


Fig. 2. Time course of cutaneous blood flow (arbitrary units A.U.) of surfactant-treated sites and control. Median values are shown ($n=12$).

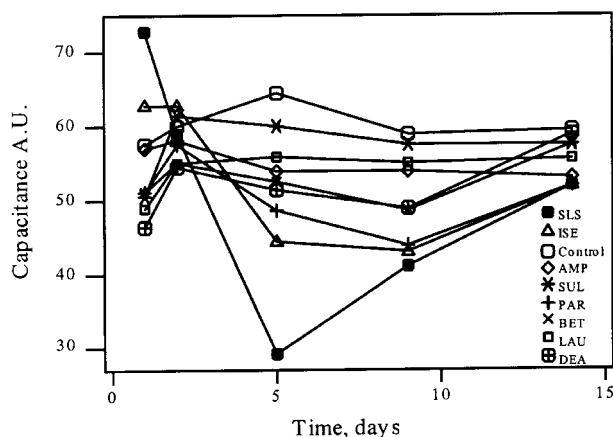


Fig. 3. Time course of skin capacitance (arbitrary units A.U.) of surfactant-treated sites and control. Median values are shown ($n=12$).

(5%) and PAR (5%). The 4th anionic, SUL (10%), was among the mildest. SLS, PAR and SUL have an equal carbon chain length of about 12, while the size of the hydrophilic group increases in this order. Thus, this increase in hydrophilic group might well explain the lower irritation potential, and substantiate previous findings on similar substances with other techniques (22, 26, 27).

The repeated multiparameter assessment of the skin condition gives a description of the quality as well as the severity of the irritant reaction. In the acute phase, TEWL was elevated, reflecting disruption of SC barrier function. Increased TEWL might be caused by direct alterations in the intercellular lipid membranes (6, 28) and/or by disruption of the keratin structure, a theory supported by in vitro data showing increased water permeability of isolated human skin after SLS exposure (29). Skin capacitance also increased im-

mediately after exposure to SLS. This is probably related to the increased TEWL, but can also be due to swelling of SC keratin proteins, exposing new water-binding sites, and for that reason an increased hydration (5, 9, 23, 30). In vitro studies also indicate that SLS is sorbed to keratin (31) and causes intense swelling (32).

In the present study, no increase in skin capacitance was found after exposure to the other substances. Instead, most of them decreased capacitance immediately after exposure. Thus, this indicates that there is no increase in water-binding sites, something that is supported in in vitro studies, where no swelling was observed after exposure to some cationics and nonionics (32). The acute phase was also characterized by the presence of intense erythema along with increased superficial blood flow, indicating an inflammatory response. However, BET, SUL and the nonionics caused no significant increase in blood flow. After exposure to SLS, increased levels of inflammatory cytokines have been found in human skin (8). This inflammatory response might influence the synthesis of new lipids, and explain the protracted TEWL enhancement following surfactant exposure (33).

After about a week, TEWL and blood flow approached normal values and almost no erythema was present. Instead, the areas exhibiting the most intense reactions turned scaly with lower capacitance values. This is in accordance with previous studies on skin reactions to surfactant-induced damage (9, 21), also verifying that the skin can be affected for more than 14 days after a single exposure of an irritant (9, 10, 33). The presence of loose scales on the skin probably results in lower capacitance values due to a decreased contact area between the skin and the probe (34), an effect earlier shown from body hair (35). The induction of late skin dryness, as measured on D 5, seems to be inversely correlated with the early skin damage, as evaluated by TEWL and blood flow measurements. Thus, no obvious differences in mechanism between the substances could be detected, indicating that the severity of the irritant reaction depends on the potency of the applied surfactant. However, some deviations were noted: the early differences in impact on skin capacitance between the surfactants and the lack of significantly increased blood flow in sites exposed to the nonionics, BET or SUL. Further studies are needed to verify the validity of the observed changes with time for other concentrations of the surfactants.

In conclusion, this study compared the time course of the skin barrier recovery following exposure to different surfactants. The surfactants produced significantly different degrees of irri-

tation, with 3 of the 4 tested anionics having the highest irritation potential. TEWL and skin blood flow exhibited a similar time course, while changes in skin capacitance were delayed and seemed to be inversely related to previous levels of TEWL and blood flow.

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