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Penetration of mixed micelles into the epidermis: Effect of mixing sodium dodecyl sulfate with dodecyl hexa(ethylene oxide)

PETER N. MOORE, ANAT SHILOACH,
SUDHAKAR PUVVADA, and DANIEL BLANKSCHTEIN,
Department of Chemical Engineering, Massachusetts Institute of Technology, Cambridge, MA 02139 (P.N.M., D.B.) and Unilever Home and Personal Care NA, Trumbull, CT 06611 (A.S., S.P.).

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Synopsis

The penetration of the anionic surfactant sodium dodecyl sulfate (SDS) into the epidermis from contacting solutions of SDS and the nonionic surfactant dodecyl hexa(ethylene oxide) ($C_{12}E_6$) was measured for three SDS concentrations (25 mM, 50 mM, and 100 mM) and three SDS solution compositions (1, 0.83, and 0.50). The addition of $C_{12}E_6$ to the SDS solutions was found to decrease the amount of SDS penetrating into the epidermis. The observed decrease occurred via two plausible mechanisms: (i) the addition of $C_{12}E_6$ decreased the SDS monomer concentration, thus reducing the driving force for the penetration of monomeric SDS into the epidermis, and (ii) the addition of $C_{12}E_6$ reduced, or prevented, the penetration of micellar SDS into the epidermis. Using dynamic light scattering, the hydrodynamic radii of the SDS/$C_{12}E_6$ micelles were determined to be 20 Å, for the α_m = 1 micelles, 24 Å for the α_m = 0.83 micelles, and 27 Å for the α_m = 0.50 micelles (where α_m denotes the SDS micelle composition). A comparison with typical stratum corneum aqueous pore radii reported in the literature (10–28 Å) suggests that the α_m = 1 (pure SDS) micelles are able to penetrate into the epidermis, while the α_m = 0.83 and the α_m = 0.50 SDS/$C_{12}E_6$ mixed micelles are sterically hindered from doing so due to their larger sizes. The observed reduced penetration of SDS into the epidermis upon the addition of $C_{12}E_6$ could lead to a reduction in the skin irritation potential of SDS, provided that there is a relationship between the concentration of SDS in the epidermis and the skin irritation induced by SDS.

INTRODUCTION

The study of why and how surfactants induce skin irritation and skin damage has broad implications, from the design of mild personal care products to assisting the transport of therapeutic drugs across the stratum corneum (SC) (1–12). Previous studies have compared the irritation potential of different surfactants (3,8,10,11,13–16), and have also determined how different surfactants can lead to changes in the permeability of the

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skin (1,2,9,17–20). Although various mechanisms have been invoked to explain surfactant-induced skin irritation, in the majority of these mechanisms the surfactant must penetrate into the skin in order to induce irritation (1,3,7,9,10,19–23). Accordingly, a simple way to reduce the skin irritation potential of a surfactant solution involves reducing the amount of surfactant that penetrates into the skin.

A widely accepted view regarding surfactant-induced skin irritation is that, at surfactant concentrations exceeding the critical micelle concentration (CMC), where surfactant micelles first form, only surfactant monomers can penetrate into the skin, either because surfactant micelles are not surface-active or because they are too large to penetrate into the SC (3,6,14,16,18,24,25). This description of surfactant monomer penetration into the skin will be referred to hereafter as the *monomer penetration model.* The monomer penetration model is based primarily on experimental observations using mixtures of surfactants, where surfactant-induced skin irritation was correlated with the CMC of the surfactant mixtures examined (6,24,26). The surfactant monomer concentration is approximately equal to the CMC (27), and therefore, according to the premise of the monomer penetration model, only the surfactant monomers should contribute to the observed surfactant-induced skin irritation.

We have recently challenged the monomer penetration model by unambiguously demonstrating that micelles of the anionic surfactant sodium dodecyl sulfate (SDS) contribute significantly to SDS penetration into the epidermis at SDS concentrations exceeding the CMC (28). The fact that SDS micelles were found to contribute to SDS penetration into the epidermis clearly contradicts the monomer penetration model, which predicts that the micellar surfactant should have no effect on surfactant penetration into the epidermis. In addition, we demonstrated that the SDS micelle contribution to skin penetration can be eliminated by mixing SDS with poly(ethylene oxide) (PEO), a nonionic polymer known to bind to SDS micelles, to form PEO-bound SDS micelles (28). To explain both findings, we proposed a new model of surfactant penetration into the skin, in which the free SDS micelles are sufficiently small to access the aqueous pores of the SC, while the PEO-bound SDS micelles are sterically hindered from doing so due to their larger size. In contrast to the monomer penetration model, the new surfactant skin penetration model highlights the potential importance of the micelles in determining surfactant penetration into the skin. If the micellar surfactant is able to penetrate into the skin, then one predicts the commonly reported dose-dependent skin irritation response to surfactants (2,3,8,13,16,18), as well as providing an explanation for the increased penetration of surfactants into the skin beyond the CMC (25,28,29). The monomer penetration model fails to predict this observed dose dependence because at surfactant concentrations exceeding the CMC, where the concentration of surfactant monomers is constant, there should be no effect of increasing the total surfactant concentration on the surfactant-induced skin irritation.

An important question that arose from our previous investigation (28) is whether mixing surfactants will have an effect on the ability of the micellar surfactant to penetrate into the skin. It is well known that mixing surfactants can lower the surfactant monomer concentration (24,30,31). In fact, the relationship observed between the reduction in the surfactant monomer concentration due to mixing surfactants and the resulting skin irritation reduction was used as the basis for the monomer penetration model (6,24,26). However, having demonstrated that the micellar surfactant can contribute to surfactant penetration into the skin (28), it became important to determine whether mixing

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surfactants could also reduce the penetration of the micellar surfactant into the skin in addition to reducing the surfactant monomer penetration. In this respect, it also became important to determine the relative contributions of the monomeric and the micellar surfactant fractions to surfactant penetration into the skin, including quantifying which one is reduced the most by mixing surfactants.

With this in mind, we measured the amount of SDS that penetrates into the epidermis from aqueous mixtures of SDS and the nonionic surfactant dodecyl hexa(ethylene oxide) ($C_{12}E_6$) after five hours of exposure. We found that SDS in SDS/$C_{12}E_6$ mixed micelles is less able to penetrate into the epidermis than SDS in pure SDS micelles. We also found that the majority of SDS penetrating into the skin from SDS/$C_{12}E_6$ mixtures results from the monomeric fraction. Dynamic light scattering (DLS) measurements indicated that mixing SDS with $C_{12}E_6$ leads to an increase in the micelle size. We propose that it is the increased micelle size that reduces, or prevents, the penetration of the SDS/$C_{12}E_6$ mixed micelles into the epidermis. Furthermore, we propose that, in general, surfactant mixtures that obey the monomer penetration model contain mixed micelles that are too large to be able to penetrate into the epidermis.

EXPERIMENTAL

MATERIALS

Sodium dodecyl sulfate (SDS) and sodium chloride (NaCl) were purchased from Sigma Chemicals (St. Louis, MO) and were used as received. Dodecyl hexa(ethylene oxide) ($C_{12}E_6$) was purchased from Nikko Chemicals (Tokyo, Japan) and was used as received. Water was produced using a Millipore Academic water filter. ^{14}C-radiolabeled SDS was purchased from American Radiolabeled Chemicals (St. Louis, MO) and was used as received. Phosphate-buffered saline (PBS) was prepared using PBS tablets from Sigma Chemicals and Millipore filtered water.

PREPARATION OF SKIN SAMPLES

Female Yorkshire pigs (40–45 kg) were purchased from local farms. Skin from the back of the pig was harvested within one hour of sacrificing the animal. The subcutaneous fat was trimmed off using a razor blade, and the full-thickness pig skin was cut into 2-cm × 2-cm pieces and stored in a −80 °C freezer until used.

EXPERIMENTAL PROTOCOL

After allowing the skin to thaw for a half hour at room temperature, the pig skin was mounted in a vertical Franz diffusion cell (Permegear Inc., Riegelsville, PA), with the SC facing the donor compartment. The donor and the receiver compartments of the diffusion cell were filled with phosphate-buffered saline (PBS; phosphate concentration of 10 mM; NaCl concentration of 137 mM; Sigma Chemical Company), and the skin was left to hydrate for one hour. The PBS in the donor compartment was removed, and 1.5 ml of surfactant solution was added to the donor compartment. The solution in the donor compartment, referred to hereafter as the *contacting solution,* contained mixtures of

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SDS and $C_{12}E_6$, each with about 0.5 μCi/ml of ^{14}C-radiolabeled SDS and 100 mM NaCl. We verified that the concentration of radiolabeled SDS in the contacting solution did not change appreciably during the five-hour exposure to the skin. A five-hour exposure was chosen because this time was sufficient to enable significant penetration of SDS into the skin, but short enough to prevent the saturation of the skin with SDS. The temperature of the diffusion cell was ambient, that is, 20° ± 1 °C.

After five hours of exposure, the contacting solution was removed, and the donor compartment was rinsed four times with 2 ml of PBS to remove any SDS that was not bound to the skin. The skin was subsequently heat-stripped by soaking it in a bath of water at 60 °C for two minutes, and the epidermis (SC and viable epidermis) was separated from the dermis. The exposed epidermis was then dried in a fume hood for two days and weighed. The dried epidermis was dissolved in 1.5 ml of Soluene-350 (Packard, Meriden, CT). Ten milliliters of Hionic Fluor scintillation cocktail (Packard) was added to the Soluene-350 after the epidermis was dissolved, and the concentration of radiolabeled SDS was determined using a Packard Tri-Carb 4350 scintillation counter. Knowing the concentration of SDS in the contacting solution, C_{SDS}, the radioactivity of the contacting solution, $C_{rad,donor}$, the dry weight of the epidermis, m, and the radioactivity of the epidermis, $C_{rad,skin}$, it was possible to determine the concentration of SDS in the dried epidermis, $C_{SDS,skin}$, using the following equation:

$$C_{SDS,\,skin} = \frac{C_{rad,\,skin} \cdot C_{SDS}}{C_{rad,\,donor} \cdot m} \tag{1}$$

DYNAMIC LIGHT SCATTERING

The SDS and the SDS/$C_{12}E_6$ solutions were prepared in Millipore filtered water with 100 mM NaCl. The 100 mM NaCl was added to the surfactant solution to screen electrostatic intermicellar interactions in the DLS measurements (32–35). To prevent dust from interfering with the light-scattering measurements, the surfactant solutions were filtered through a 0.02-μm Anotop 10 syringe filter (Whatman International, Maidstone, England) directly into a cylindrical-scattering cell, and sealed until use. DLS was performed at 25 °C and a 90° scattering angle on a Brookhaven BI-200SM system (Brookhaven, Holtsville, NY) using a 2017 Stabilite argon-ion laser (Spectra Physics) at 488 nm. The autocorrelation function was analyzed using the CONTIN program provided by the BIC dynamic light scattering software (Brookhaven, Holtsville, NY), which determined the effective hydrodynamic radius, $\overline{R}_h$, using the Stokes-Einstein relation (36):

$$\overline{R}_h = \frac{k_B T}{6\,\pi\eta\overline{D}} \tag{2}$$

where k_B is the Boltzmann constant, T is the absolute temperature, η is the viscosity of the salt solution, and $\overline{D}$ is the mean diffusion coefficient of the scattering species. In order to eliminate the effects of intermicellar interactions when measuring the hydrodynamic radii of the micelles, the effective hydrodynamic radii were determined at several different total surfactant concentrations having a fixed solution composition, and the average effective hydrodynamic radii were extrapolated to a zero micelle concentration (32–35,37).

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MICELLIZATION BEHAVIOR OF THE SDS/$C_{12}E_6$ SURFACTANT MIXTURES

In this paper, α_x denotes the fraction of the total surfactant that is SDS, referred to as the SDS composition, and is defined as follows:

$$\alpha_x = \frac{[SDS]_x}{[SDS]_x + [C_{12}E_6]_x} \tag{3}$$

where $[SDS]$ denotes the concentration of SDS, $[C_{12}E_6]$ denotes the concentration of $C_{12}E_6$, and the subscript x refers to the monomeric fraction (x = 1), to the micellar fraction (x = m), or to the overall solution (x = s). Accordingly, α_s = 0.83 implies that 83% of the surfactant in the contacting solution is SDS, and that the remaining 17% (1 − α_s = 0.17) is $C_{12}E_6$. Recently developed molecular-thermodynamic theories of micellization (30,31) were used to predict the micellization behavior of the SDS/$C_{12}E_6$ surfactant mixtures. Specifically, the concentration and the composition of the surfactant monomers and of the mixed micelles were predicted as a function of the total surfactant concentration and solution composition. The resulting predicted values of α_1, α_m, and the total surfactant monomer concentration, C_1, for the contacting solutions examined are reported in Tables I and II.

RESULTS AND DISCUSSION

EFFECT OF ADDING $C_{12}E_6$ AT A FIXED SDS CONCENTRATION ON THE PENETRATION OF SDS INTO THE EPIDERMIS

It is well known that when two surfactants that interact synergistically are mixed, the surfactant mixture often exhibits lower skin irritation than either of the individual surfactants (6,24,26). It is also known that SDS and $C_{12}E_6$ interact synergistically to reduce the CMC of the surfactant mixture (30,31). SDS is a model skin irritant (10,13,15,16,26,38), while $C_{12}E_6$ is thought to be a mild surfactant, although it may lead to skin dryness (3,39). The system of SDS and $C_{12}E_6$ was chosen as a model surfactant mixture because of the synergy that it exhibits, as well as because the skin irritation potential of this surfactant mixture is expected to result primarily from the action of the irritating surfactant, SDS. This, in turn, allows us to relate the penetration of SDS into the epidermis to skin irritation, while neglecting the irritation potential of $C_{12}E_6$.

Evidence for the relationship between the concentration of SDS in the epidermis and the skin irritation induced by SDS was presented in our recent paper (28), in which the concentration of SDS in the epidermis was observed to be dose-dependent for α_s = 1,

Table I

Predicted Values of α_1 and α_m for Mixtures of SDS and $C_{12}E_6$ in 0.1 M NaCl at the Various SDS Concentrations and Solution Compositions (α_s) Used for the SDS Skin Penetration Experiments (30,31)

	25 mM SDS	50 mM SDS	100 mM SDS
α_s	α_1, α_m	α_1, α_m	α_1, α_m
1	1, 1	1, 1	1, 1
0.83	0.96, 0.83	0.96, 0.83	0.96, 0.83
0.50	0.925, 0.50	0.925, 0.50	0.925, 0.50

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Table II
Predicted Total Surfactant Monomer Concentration, C_1 (mM), for the Mixtures of SDS and $C_{12}E_6$ in 0.1 M NaCl at the Various SDS Concentrations and Solution Compositions (α_s) Used for the SDS Skin Penetration Experiments (30,31)

α_s	25 mM SDS	50 mM SDS	100 mM SDS
1	0.850	0.864	0.877
0.83	0.683	0.695	0.707
0.50	0.266	0.270	0.276

corresponding to the dose-dependent SDS skin irritation potential observed by other researchers (2,3,8,13,16,18). However, it should be noted that, in this paper, we have not measured the amount of $C_{12}E_6$ that penetrates into the epidermis. Therefore, we did not ascertain whether the interaction between $C_{12}E_6$ and the SC is indeed mild. In this respect, experiments by de la Maza *et al.* have shown that nonionic surfactants can have a strong effect on reducing the barrier properties of SC lipid bilayers (19,40). However, other researchers have observed that nonionic surfactants tend to have a smaller effect on the skin than SDS (3,39,41). Therefore, although the assumption that $C_{12}E_6$ is benign irritation-wise may not be entirely accurate, it is expected that the skin irritation potential of SDS should overwhelm that of $C_{12}E_6$. An investigation of the skin irritation potential of $C_{12}E_6$ is underway, and the results of this investigation will be reported elsewhere.

Based on the premise that the skin irritation induced by SDS is related to the concentration of SDS in the epidermis, we measured whether adding $C_{12}E_6$ to a fixed SDS concentration (50 mM) in the contacting solution would reduce the concentration of SDS in the epidermis after five hours of exposure, C_{skin}, and consequently, reduce the skin irritation potential of the surfactant solution. The purpose of conducting the experiments at a fixed SDS concentration is to ensure that any observed decrease in C_{skin} upon the addition of $C_{12}E_6$ would not result from the decrease in the total SDS concentration in the contacting solution, but instead would be related to changes in the solution behavior of SDS. Figure 1 shows that as α_s is decreased by adding more $C_{12}E_6$ to the contacting solution, C_{skin} decreases. The observed decrease in C_{skin} as α_s decreases is consistent with reported observations of the reduced skin irritation potential of surfactant mixtures, provided that C_{skin} is related to the observed skin irritation (6,24,26).

EFFECT OF INCREASING α_s ON THE ABILITY OF MICELLAR SDS TO PENETRATE INTO THE EPIDERMIS

There are two plausible mechanisms responsible for the decrease in C_{skin} observed in Figure 1: (i) the addition of $C_{12}E_6$ reduces the SDS monomer concentration, as predicted by the monomer penetration model, and (ii) the addition of $C_{12}E_6$ reduces the ability of the micellar SDS to penetrate into the epidermis, as predicted by our recently proposed micelle penetration model (28). It is entirely possible for both mechanisms to act simultaneously. In view of that, we conducted the following experiments to clarify whether mechanism (ii) was involved in the reduction of C_{skin} observed in Figure 1.

We tested whether mixed micelles present in the SDS/$C_{12}E_6$ surfactant mixtures could

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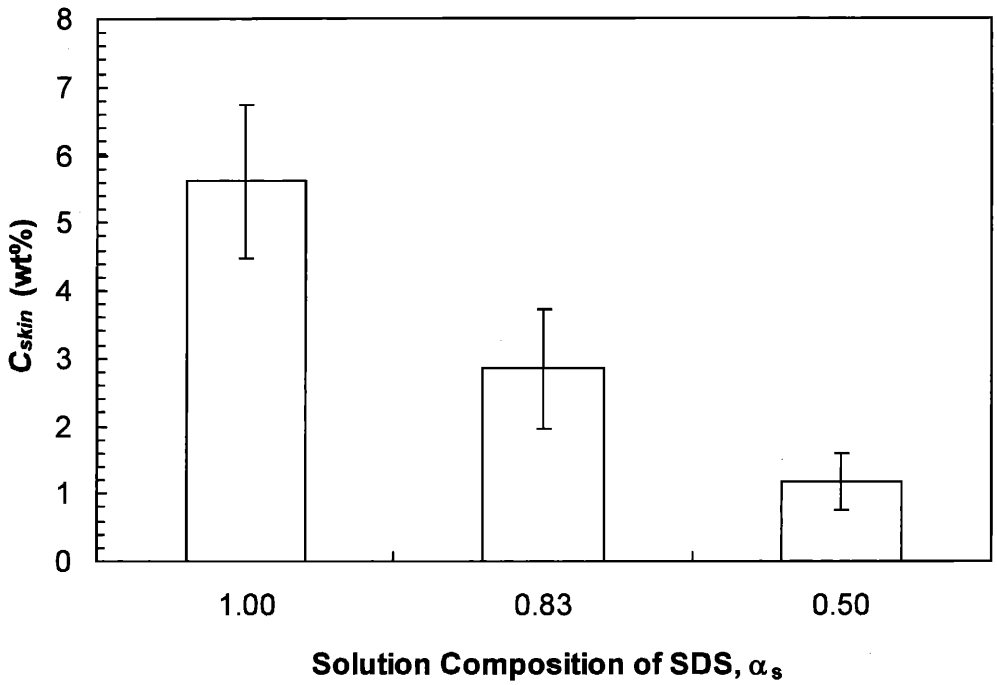

Figure 1. The effect of decreasing the composition of SDS, α_s, in the contacting solution on the concentration of SDS in the epidermis after a five-hour exposure (C_{skin}) to solutions containing 50 mM SDS and increasing concentrations of $C_{12}E_6$. The error bars reflect a 95% confidence interval based on six samples of each composition.

penetrate into the epidermis by maintaining a constant α_s value and increasing the total surfactant concentration in the contacting solution. In general, the ability of micelles to penetrate into the skin can be determined by measuring how increasing the total surfactant concentration beyond the CMC, at a fixed α_s value, affects the amount of surfactant penetrating into the epidermis (28). If the surfactant concentration in the epidermis is found to increase, then surfactant in micellar form contributes to surfactant penetration into the epidermis. Conversely, if the surfactant concentration in the epidermis is found to remain constant, then surfactant in micellar form does not contribute to surfactant penetration into the epidermis, in which case the surfactant penetration should obey the monomer penetration model.

The SDS/$C_{12}E_6$ surfactant mixtures that were investigated had solution compositions of α_s = 1, 0.83, and 0.50. Figure 2 shows the effect of increasing the total SDS concentration in the contacting solution (from 25 mM to 100 mM) on C_{skin} at these three fixed α_s values. As shown in Tables I and II (30,31), for each value of α_s over the range of surfactant concentrations examined, $\alpha_m = \alpha_s$, α_1 is constant and C_1 is approximately constant. Therefore, any observed increase in C_{skin} as the total SDS concentration increases for each α_s value examined can only be attributed to the penetration of micellar SDS into the epidermis, because only the micelle concentration is increasing. (Recall that the SDS monomer concentration is equal to $\alpha_1 C_1$, which remains constant, while the concentration of SDS in micellar form is equal to $\alpha_m(C_t - C_1)$, where C_t is the total surfactant concentration, which increases in this case.)

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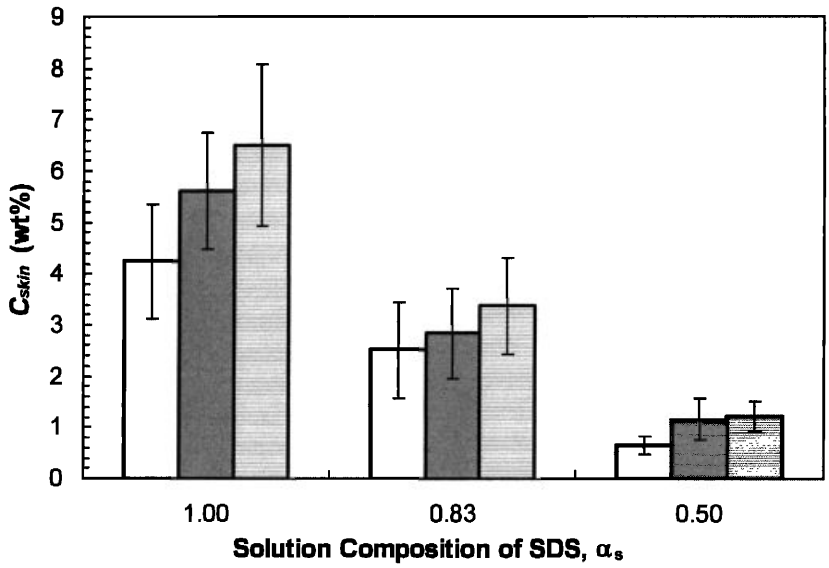

Figure 2. The effect of increasing the SDS concentration in the contacting solution on the concentration of SDS in the epidermis after a five-hour exposure (C_{skin}). For each composition (α_s = 1, 0.83, and 0.50), the concentrations of SDS in the contacting solution are 25 mM (empty bars), 50 mM (solid bars), and 100 mM (striped bars). The error bars reflect a 95% confidence interval based on six samples at each SDS concentration.

The increase in C_{skin} with increasing total SDS concentration observed in Figure 2 for α_s = 1, 0.83, and 0.50 clearly indicates that the micelles present in these solutions do contribute to SDS penetration into the epidermis, with their contribution decreasing as α_s decreases. Specifically, by comparing the observed increase in C_{skin} as the SDS concentration in the contacting solution is increased from 25 mM to 100 mM (ΔC_{skin}) for each α_s value examined, it is clear that the pure SDS micelles (α_s = 1) contribute more to C_{skin} ($\Delta C_{skin} \approx 0.08$) than the mixed micelles corresponding to α_s = 0.83 ($\Delta C_{skin} \approx 0.03$) and to α_s = 0.50 ($\Delta C_{skin} \approx 0.02$). This is clear evidence that changing α_s, and hence α_m, can affect the ability of the micellar SDS to penetrate into the epidermis, because for each α_s value examined, the SDS concentration in the contacting solution increases by the same amount (from 25 to 100 mM), but the effect on ΔC_{skin} is found to decrease as α_s is decreased. Although this simple analysis, based on the experimental results presented in Figure 2, clearly demonstrates that adding $C_{12}E_6$ to the SDS solution reduces the ability of the micellar SDS to penetrate into the epidermis, as proposed in mechanism (ii), a more quantitative analysis, presented below, is required to determine the contributions of mechanisms (i) and (ii) to SDS skin penetration. It should be kept in mind that the ability to reduce the penetration of the micellar SDS into the skin by mechanisms (i), (ii), or both should have a pronounced effect on reducing the skin irritation induced by SDS.

We have recently demonstrated that the contribution of the micellar SDS to C_{skin} is comparable to the contribution of the monomeric SDS at low SDS concentrations (28). However, because the concentration of SDS micelles increases as the total SDS concentration increases beyond the CMC, while the concentration of SDS monomers remains constant, we concluded (28) that it is the penetration of the micellar SDS that leads to

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the dose-dependent skin irritation response observed by many researchers (2,3,8,13,16,18). Indeed, we found that the SDS micellar contribution overwhelms the SDS monomeric contribution at the higher SDS concentrations (28). Accordingly, reducing, or preventing, the contribution of the micellar surfactant to C_{skin} by mixing surfactants should lead to a reduction in the skin irritation potential of the surfactant mixture, in addition to any beneficial effect due to a reduction in the surfactant monomer concentration.

REGRESSION ANALYSIS OF THE CONTRIBUTIONS OF MICELLAR AND MONOMERIC SDS TO C_{skin} FROM SOLUTIONS OF SDS/$C_{12}E_6$

Figure 2 shows that as α_s decreases, the contribution of the SDS/$C_{12}E_6$ mixed micelles to C_{skin} decreases. To quantify the relative contributions of SDS in mixed micelle form (α_m = 1, 0.83, and 0.50) and in monomeric form to C_{skin}, we carried out a multiple linear regression analysis using all the experimental data, prior to averaging, that was used to generate Figure 2. The simplest relationship between the SDS concentrations in micellar and monomeric form to C_{skin} is a linear one. The basis for this linear relationship is that in Fickian diffusion from an infinite reservoir with a large concentration difference, the net permeant flux at a given time is directly proportional to the initial permeant concentration (42). With this assumption in mind, we fitted C_{skin} to the following expression:

$$C_{skin} = \alpha \cdot C_{1,SDS} + b \cdot C(\alpha_m = 1) + c \cdot C(\alpha_m = 0.83) + d \cdot C(\alpha_m = 0.50) \qquad (4)$$

where *a, b, c,* and *d* are the regression coefficients that were determined from the regression analysis, $C_{1,SDS}$ is the SDS monomer concentration, $C(\alpha_m)$ is the SDS concentration in micelles of composition α_m, and C_{skin} is the SDS concentration in the epidermis (in units of mmols of SDS per gram of dry epidermis). For the regression analysis, $C_{1,SDS} = \alpha_1 C_1$ and $C(\alpha_m) = \alpha_m(C_t - C_1)$ using the appropriate values of α_1, α_m, and C_1 reported in Tables I and II (30,31). In this manner, we were able to isolate the contributions to C_{skin} due to the micellar SDS for the three micelle compositions examined (reflected in *b, c,* and *d*), as well as due to the monomeric SDS (reflected in *a*). The following values of *a, b, c,* and *d* were obtained from the regression analysis:

$a = 4.1 \pm 1.0\ C_{skin}/C_{1,SDS}$
$b = 0.032 \pm 0.014\ C_{skin}/C(\alpha_m = 1)$
$c = 0.003 \pm 0.012\ C_{skin}/C(\alpha_m = 0.83)$
$d = 0.0009 \pm 0.0092\ C_{skin}/C(\alpha_m = 0.50)$

According to these regression results, the α_m = 0.50 micelles do not contribute to C_{skin} at all, because *d* is essentially equal to zero. The α_m = 0.83 micelles contribute very little or not at all to C_{skin}, because although the average value of *c* is not zero, the 95% confidence interval includes zero. On a per SDS molecule basis, the contribution of the SDS monomers is quite large, with one SDS molecule in monomeric form being 130 times more skin penetrating than one SDS molecule in a pure SDS micelle (α_m = 1). However, at the higher SDS concentrations, there is significantly more micellar SDS than monomeric SDS, and as a result, the net contribution to C_{skin} due to the micellar SDS may overwhelm that due to the SDS monomers.

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To more clearly describe the relative contributions of the monomeric SDS and the micellar SDS to skin penetration, Figure 3(a–c) shows the total contributions of the monomeric and the micellar fractions of SDS to C_{skin} for α_s = 1, 0.83, and 0.50 respectively, based on the regression data given above. Specifically, the SDS monomeric contribution to C_{skin} is $a \cdot C_{1,SDS}$, and the three micellar contributions to C_{skin} are $b \cdot C(\alpha_m = 1)$, $c \cdot C(\alpha_m = 0.83)$, and $d \cdot C(\alpha_m = 0.50)$. Figure 3(a–c) clearly shows that the SDS monomers make a contribution to C_{skin} that is larger than that of the micellar SDS for the three α_s values examined, as seen by the empty bars (representing the monomeric contribution) always being larger than the solid bars (representing the micellar contribution). It is only for α_s = 1, the pure SDS case, that the micelles make a large contribution to C_{skin}, particularly at the highest surfactant concentrations examined (see Figure 3a). In Figures 3b and 3c, which correspond to the α_s = 0.83 and 0.50 surfactant mixtures, respectively, the micellar contribution is almost non-existent. Indeed, considering the confidence interval for the coefficients *c* and *d*, it is apparent that the micellar contributions include the possibility of a zero contribution to C_{skin}. Therefore, the monomer penetration model represents a reasonable approximation for the two SDS/$C_{12}E_6$ surfactant mixtures examined, where the micellar SDS does not penetrate appreciably into the epidermis for the SDS concentrations examined (25, 50, and 100 mM). However, the reduction in C_{skin} observed with decreasing α_s, shown in Figures 1 and 2, results from both the reduction in the SDS monomer concentration and the reduction in the ability of the micellar SDS to penetrate into the epidermis.

Generalizing the observations made in the case of the SDS/$C_{12}E_6$ surfactant mixtures to other surfactant mixtures, it is plausible that the observed reduction in skin irritation upon mixing surfactants reported by several researchers occurs because *both the monomeric and the micellar surfactant penetrations into the skin are diminished* (6,24,26). At the high total surfactant concentrations commonly utilized in commercial surfactant products, the micellar contribution can be quite large, as demonstrated by the dose-dependent surfactant-induced skin irritation results reported in the literature (2,3,8,13,16,18). Consequently, any reduction in the ability of the micellar surfactant to penetrate into the skin, as reflected by lower values of the regression coefficients (such as *b, c,* and *d*), should have a significant impact on C_{skin} at high total surfactant concentrations. In other words, reducing the micellar contribution to C_{skin} should lead to a reduction in the skin irritation potential of the surfactant system contacting the skin.

DYNAMIC LIGHT SCATTERING DETERMINATION OF SDS/$C_{12}E_6$ MIXED MICELLE SIZES

In Figure 4, the hydrodynamic radii of the SDS/$C_{12}E_6$ mixed micelles are determined using DLS by extrapolating the effective hydrodynamic radii of these micelles to a zero micelle concentration. At the surfactant concentrations corresponding to Figure 4, α_m is predicted to be approximately equal to α_s, and therefore, one can treat the micelles as having a constant α_m value over the entire surfactant concentration range examined (see Table I). This is important, because a change in α_m could lead to a change in the hydrodynamic radii of the micelles. (The hydrodynamic radii of the micelles determined using this method are reported in Table III.) According to the surfactant penetration model advanced in our recent paper (28), the size of the micelle determines its ability to penetrate into the SC. (Note that the discussion in the following section introduces the caveat that electrostatic interactions may also play a role.) The micelle penetration

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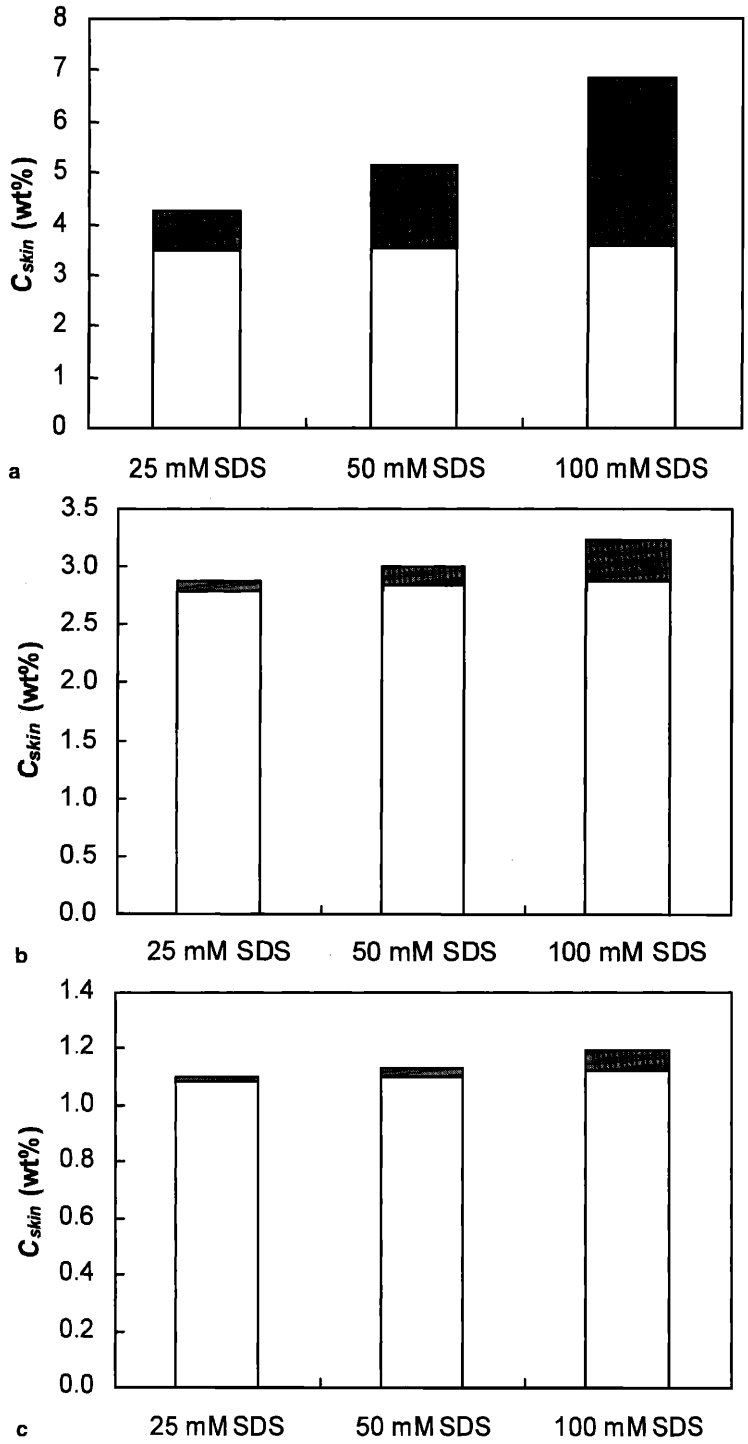

Figure 3. The contribution of monomeric SDS (open bars) and micellar SDS (solid bars) to C_{skin} calculated using the results of the multiple linear regression analysis for: (a) $\alpha_s = 1$, (b) $\alpha_s = 0.83$, and (c) $\alpha_s = 0.50$. Adding up the contributions from the two bars yields the combined contribution of the SDS monomers and the micellar SDS to C_{skin}. Note that the vertical axes in a–c are scaled differently.

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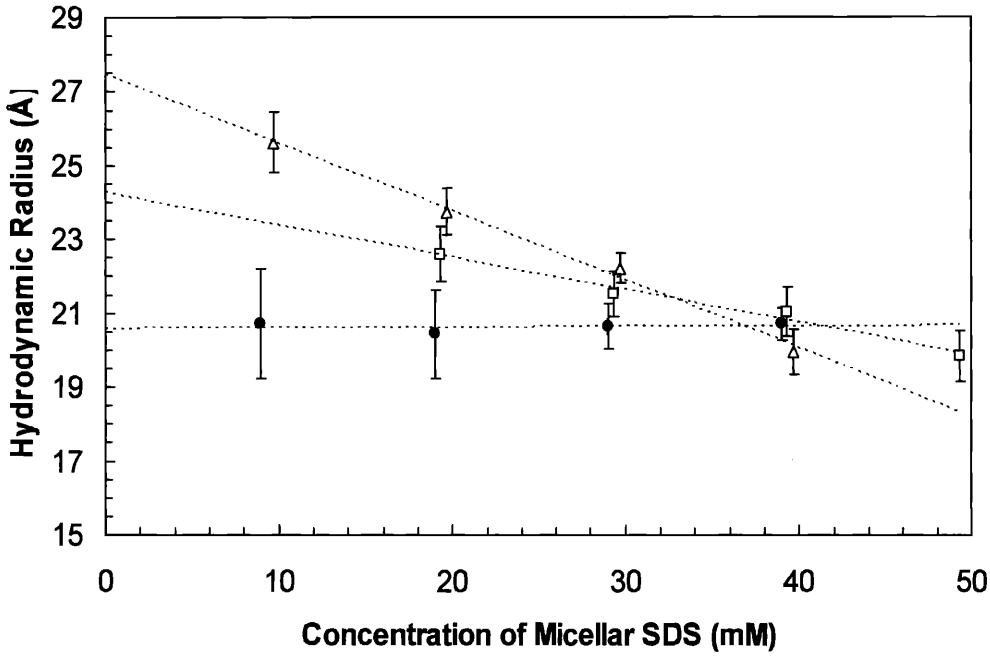

Figure 4. Measured effective hydrodynamic radii of SDS/$C_{12}E_6$ mixed micelles for α_m = 1 (●), α_m = 0.83 (□), and α_m = 0.50 (△) as a function of the concentration of micellar SDS (that is, the SDS concentration minus the predicted SDS monomer concentration $\alpha_1 C_1$; see Tables I and II) (30,31) using DLS at 25°C in 0.1 M NaCl. The micellar radii were determined using a CONTIN analysis. The error bars reflect a 95% confidence interval based on eight samples at each SDS concentration. The actual hydrodynamic radius is equal to the intercept.

Table III
The Micelle Hydrodynamic Radii Determined Using a CONTIN Analysis of the Correlation Function

α_s	R_H (Å)
1	20 ± 1
0.83	24 ± 1
0.50	27 ± 3

The actual hydrodynamic radius of the micelle is determined by extrapolating the effective hydrodynamic radii in Figure 3 to a zero micelle concentration. The error values reflect a 95% confidence interval.

model is based on the premise that only micelles that are small enough to access the aqueous pores in the SC can contribute to surfactant penetration into the epidermis. Other researchers have determined the average aqueous pore radius in the skin using permeability and/or conductivity measurements in the context of hindered-transport theories, and have reported radii values between 10 Å and 28 Å (9,12,43–45).

Based on the micelle hydrodynamic radii reported in Table III and a purely steric model of micelle penetration into the skin that ignores electrostatic interactions (discussed below), and considering a skin aqueous pore radius of at most 28 Å, the α_m = 1 micelles should be able to penetrate into the SC more easily than the α_m = 0.83 and the α_m = 0.50 micelles. This conclusion is consistent with the results of the multiple linear regression

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analysis presented above, and lends greater validity to the idea put forward by us recently (28) that steric factors can play a key role in determining whether the micellar surfactant can penetrate into the skin. Concerns that the penetration of SDS into the SC may alter the characteristic pore size in the SC are mitigated by the work of Peck *et al.* (9). These authors found that the average pore size of the SC measured by hindered transport was unaffected by exposing the epidermis to SDS solutions for 18 hours. Instead, they concluded that the increased permeability of the skin resulted from an increase in the effective porosity/tortuosity of the SC. Nevertheless, we believe that additional research should be conducted to better understand the effect of surfactant penetration into the skin on the aqueous pathways of the SC.

POSSIBLE ELECTROSTATIC EFFECTS ON SDS SKIN PENETRATION

Interestingly, the $\alpha_m = 1$ micelles have an equal, or slightly lower value, of the regression coefficient, b (0.032 ± 0.014), than the one reported in our recent paper (0.043 ± 0.006) (28), while the SDS monomers penetrate into the epidermis much more readily according to the results reported in this paper ($a = 4.1 \pm 1.0$ here versus $a = 0.14 \pm 0.04$ in reference (28)). The main difference in the conditions corresponding to the two sets of experiments is the presence of 0.1 M NaCl in the systems examined in this paper, compared to the no-added-salt case considered in the previous paper (28). It is known that the skin carries a net negative charge (9), and that the addition of salt screens this negative charge. Screening the negative charge would make it easier for negatively charged SDS monomers to approach the skin surface, which could explain the observed increase in the value of a. However, the same argument should apply to the $\alpha_m = 1$ micelles, which are also negatively charged. Nevertheless, the SDS micelles do not show a significant change in their contribution to SDS penetration upon the addition of salt. In fact, the pure SDS micelles appear to be somewhat less able to contribute to C_{skin} in the presence of salt ($b = 0.0032$) than in the absence of salt ($b = 0.0043$ in reference (28)). It is important to keep in mind, however, that the addition of salt may lead to some micelle growth (32,46). As a result, applying our model of micelle penetration, the larger micelles in the presence of salt may be less able to penetrate into the skin, thus counteracting the effect of any decrease in the electrostatic repulsions between the skin and the SDS micelles.

The discussion above about potential electrostatic effects affecting surfactant penetration into the skin indicates that steric hindrance may not be the only factor determining whether a micelle can penetrate into the aqueous pores of the skin. Iontophoresis experiments with charged permeants have shown that the aqueous pores in the SC are charged, and that positively charged permeants traverse the skin more easily than negatively charged permeants (9,44). However, it is also known that the size of the permeant relative to that of the aqueous pore affects the penetration of the permeant into the skin (9,43). If the permeant is larger than the aqueous pore size, then electrostatic effects should be irrelevant, since the steric hindrance would prevent any access into the pore. However, when the permeant is physically small enough to access the skin aqueous pores, then the electrostatic interactions between the permeant and the pores, as well as the steric interactions between the permeant and the pore wall, will play a role in the transport of the permeant across the skin (9,12,43,45,47).

In our experiments, all the micelles are negatively charged due to the presence of SDS,

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but the surface charge density of the SDS/$C_{12}E_6$ mixed micelles decreases as α_m decreases. This reduction in surface charge density should make it easier for the less negatively charged mixed micelles to access the negatively charged skin pores. However, the addition of $C_{12}E_6$ also causes the micelles to grow and sterically hinders their access to the skin pores, thereby counteracting this surface charge reduction effect. Future work aimed at studying the effect of electrostatics on permeant penetration into the epidermis should examine the penetration of fixed-size charged species at different ionic strengths.

CONCLUSIONS

It is well known that mixing surfactants can lead to a reduction in the skin irritation potential of a surfactant system (6,24,26). Based on the premise that the irritating surfactant must penetrate into the skin to induce skin irritation, we tested whether mixing the irritating surfactant SDS with $C_{12}E_6$ affected the amount of SDS penetrating into the epidermis (C_{skin}). We found that increasing the concentration of $C_{12}E_6$ in the contacting solution, while maintaining a fixed concentration of SDS, led to a decrease in C_{skin}. Provided that the skin irritation induced by SDS is related to C_{skin}, these findings are consistent with the expectation of reducing skin irritation by mixing surfactants.

In our recent paper (28), we found that both monomeric and micellar SDS are able to penetrate into the epidermis. An important consideration in the case of SDS/$C_{12}E_6$ surfactant mixtures was whether the reduction in the amount of SDS penetrating into the epidermis was due to the reduced SDS monomer concentration and/or due to a reduction in the skin penetration ability of micellar SDS. A regression analysis, based on our experimental results, demonstrated that only pure SDS micelles (α_m = 1) contributed to C_{skin} at a level comparable to the contribution of the SDS monomers, particularly at the highest surfactant concentrations examined (see Figure 3a). For the SDS/$C_{12}E_6$ surfactant mixtures, corresponding to mixed micelles having compositions of α_m = 0.83 and 0.50, the monomeric SDS contributed significantly more to skin penetration than the micellar SDS, which essentially did not contribute to C_{skin} (see Figures 3b and 3c). Consequently, mixing SDS with $C_{12}E_6$ reduced C_{skin} both by reducing the concentration of monomeric SDS and by almost entirely preventing micellar SDS from penetrating into the epidermis.

Using DLS measurements, we demonstrated that the average hydrodynamic radii of the SDS/$C_{12}E_6$ mixed micelles increased as the solution composition of SDS decreased. This corresponded to the observed decreased ability of the SDS/$C_{12}E_6$ mixed micelles to penetrate into the SC. Comparing the hydrodynamic radii of the SDS/$C_{12}E_6$ mixed micelles examined (24 Å for α_m = 0.83 and 27 Å for α_m = 0.50) with the hydrodynamic radii of the PEO-bound SDS micelles in our previous paper (25 Å, in reference (28)), the steric hindrance model for the prevention of micelle penetration into the skin remains consistent with our experimental findings in this paper, with SDS in the larger mixed micelles not contributing to C_{skin}.

From our results, one can understand how the monomer penetration model was derived from mixed-surfactant skin irritation data. Mixing surfactants often leads to growth in micelle size (30,31). When the mixed micelles cannot penetrate into the skin, then the surfactant penetration mechanism reduces to the monomer penetration model. In that case, since the CMC is comparable to the surfactant monomer concentration, there

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is a direct correlation between the CMC and the observed skin irritation. However, preventing the micellar SDS, or for that matter any micellar surfactant, from penetrating into the skin has a pronounced effect on skin irritation, because it should eliminate the dose-dependent behavior commonly observed for pure surfactant systems (2,3,8,13,16,18). Once the micelles are prevented from penetrating into the skin, the only other mechanism to reduce C_{skin} involves a reduction in the surfactant monomer concentration.

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