Surface Activity and Cutaneous Effects of Monoalkyl Phosphate Surfactants

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ABSTRACT

Monoalkyl phosphates of high purity were synthesized and were investigated for their surface-active properties and cutaneous effects. It has been found that these surfactants possess adequate surface-active properties similar to those of common anionic surfactants and that they exhibit considerable safety on the skin in comparison with typical anionic surfactants used commercially.

INTRODUCTION

The quantity of various surfactants consumed for household uses has increased every year, and contact with the skin occurs frequently. Since it is known (1-6) that surfactants present in household preparations have a distinct potential to irritate or roughen the skin, their increased use causes an increase in the incidence of dermatological problems such as hand roughness. It is, therefore, worthwhile to develop surfactants with a less damaging effect on the skin.

Evidence has been presented (2,3,5,6) that the skin irritation inducing effect of surfactants depends on their chemical structure. Many papers (1,2,4,5-7) describing irritant response caused by the surfactants have indicated that generally there is a tendency for the surfactants with high washing efficiency to exhibit a marked capacity to irritate or to roughen the skin, whereas reduction of skin damaging effect by modification of the surfactant seems to lead to a drastic impairment in detergency.

In this study, whose objective was the combination of both properties, we synthesized high purity monoalkyl phosphates and evaluated them with respect to various characteristics concerning detergency and cutaneous reaction.

EXPERIMENTAL PROCEDURES

Preparation of Monoalkyl Phosphates

The appropriate alcohol (1 mole) was added dropwise to phosphoryl chloride (1 mole) with vigorous stirring to maintain the reaction temperature of about 25 C. Hydrogen chloride, which was evolved during this process, was removed from the reaction mixture under reduced pressure. The reaction mixture was continuously agitated over a period of about 1 hr. Then, the temperature was raised to about 50 C and maintained at this temperature for 5 hr. The monoalkyl phosphoryl dichloride thus obtained was poured dropwise into a large excess of cold water and stirring was continued for 5 hr at 30 C. After cooling to room temperature, ether was added, and the organic layer was separated. Evaporation of the ether gave a white crystalline product containing only monoalkyl phosphate. Purities of these compounds which were determined by elemental analysis were as follows: monooctyl phosphate (C_8 MAP): 97.23%, monodecyl phosphate (C_{10} MAP): 99.61%, monolauryl phosphate (C_{12} MAP): 99.45%, monomyristyl phosphate (C_{14} MAP): 100%, monocetyl phosphate (C_{16} MAP): 99.83%, monostearyl phosphate (C_{18} MAP: 97.60%, monooleyl phosphate (C_{18}^{Δ} MAP): 98.40%.

Preparation of salts: sodium and triethanolamine (TEA) salts of the monoalkyl phosphates were prepared by neutralizing the phosphates in ethanol with appropriate amounts of the corresponding base. The salts were crystallized from the solution on evaporation of the solvent and dried under vacuum. Mono, sesqui, and disodium and TEA salts were prepared by neutralization with required amounts of sodium hydroxide or TEA.

Other Surfactants

Alkyl sulfate (AS) ($C_nH_{2n+1}OSO_3Na$ [C_nAS]), alkyl polyoxyethylene sulfate (ES) ($C_nH_{2n+1}(CH_2CH_2O)_pSO_3Na$ [C_n-pES]), alkyl benzene sulfonate (LAS) (C_nH_{2n+1}  SO_3Na[C_nLAS]), alfa olefin sulfonate (AOS) ($C_{n-3}H_{2n-5}CH_2$-CH=CHSO_3Na and $C_{n-3}H_{2n-5}CH(OH)$-$CH_2CH_2SO_3Na$[C_nAOS]), paraffin sulfonate (SAS) ($C_nH_{2n+1}SO_3Na$[C_nSAS]), sodium carboxylate ($C_{n-1}H_{2n-1}$ COONa[C_nSoap]), alkyl polyoxyethylene (EO) ($C_nH_{2n+1}O(CH_2CH_2O)_pH$[$C_n$-pEO]), and monoalkyl acylglutamate (AGS) (C_nH_{2n+1}CONHCH(COOH)-CH_2CH_2COONa[C_nAGS]) are identical with those reported previously (5,6,8-10).

Measurements of Physicochemical Properties

The water solubility of the surfactants was measured in the following manner; aqueous solutions of a surfactant at various concentrations were heated or cooled; the clear point at which the appearance of the solution changed from opaque to transparent, or the cloud point at which it changed from transparent to turbid were found by visual observation. Krafft points of surfactants were estimated from the temperature at which an abrupt change in conductivity occurred. Surface tension of the aqueous solution of the compounds was measured with a DuNouy tensiometer in the range of 0.001 to 0.5 mole/l at 25 C or 40 C. The CMC values were determined by measuring the equivalent conductivity (11) of aqueous solution of surfactants. Foam height, foam stability, and foam density of the aqueous solution of surfactants were measured by the Ross and Miles method (12). Foam height was recorded immediately (A) and at 10 min (B). Foam stability and foam density were calculated as ratios of B to A and of the foam weight to the corresponding volume.

Defatty Measurements

A mixture including triolein (10 g), cholesterol (5 g), squalene (5 g), palmitic acid (5 g) and Sudan Black-acidic dye (0.2 g) was employed as a substitute for oily soil. This mixture was dissolved in 25 ml of chloroform at 40 C, then deposited on glass slides (2.6 x 7.6 cm) at a level of 0.4 ± 0.05 g of the oil mixture per six glass slides. The washing apparatus consisted of a plastic holder equipped for six glass slides which was placed in a beaker with a central propeller (35 mm) made of stainless steel (Fig. 1). Washing was performed with 900 ml of surfactant solution for 10 or 30 min at 40 ± 1 C and at 1300 ± 50 rpm of propeller rotation. After washing, the glass slides were rinsed by immersion in ion-exchanged water and dried in a desiccator for 24 hr to measure decrease in weight of the oil mixture on the six glass slides. Furthermore, the oil mixture

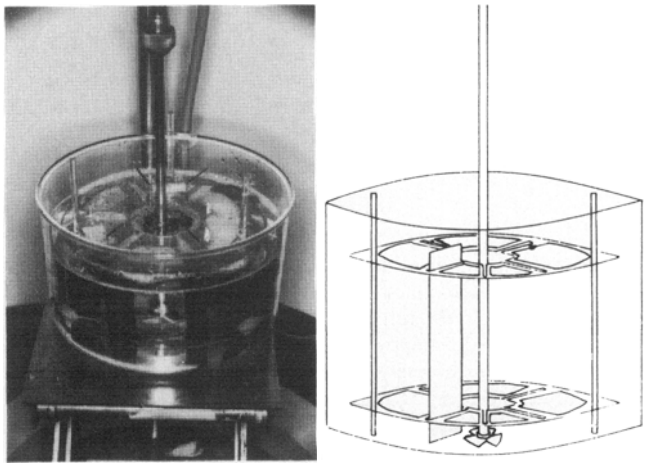

FIG. 1. Apparatus for evaluating oil removal power of surfactants.

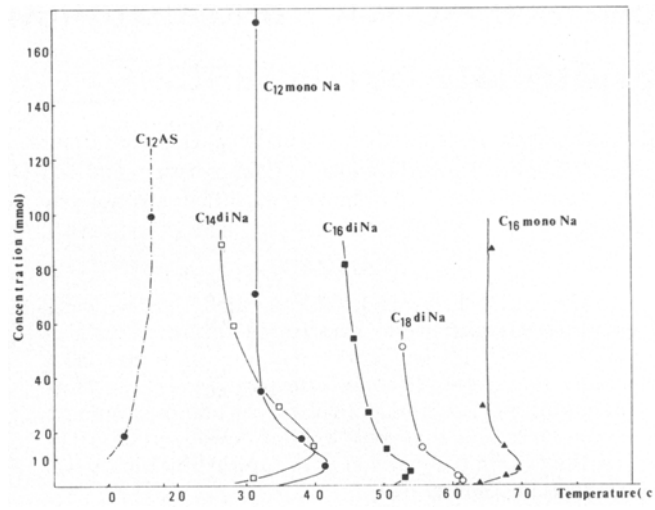

FIG. 2. Solubility-temperature curve of monoalkyl phosphates.

adhering to the six glass slides was extracted with 100 ml of ethanol, and defatty potential was determined by measuring spectrophotometrically the absorbance at 590 nm of solubilized Sudan Black.

Measurements of Optical Rotation

All procedures were made as previously reported (8). Bovine serum albumin (BSA) and surfactant solutions were prepared by using ion-exchanged water and mixed to 1.0 g/100 ml and 0.1-1,5 g/100 ml concentrations, respectively. To ensure complete interaction, the mixed solutions were allowed to stand overnight at 30 C, and then optical rotation of the solutions was measured with Model DIP-SL automatic polarimeter at 589 nm and 23 C. Specific rotation was calculated by applying the optical rotation value by the equation $[\alpha]_D = 100 \times \alpha / d \times c$, where α d, and c are optical rotation, cell length (dm), and BSA concentration, respectively.

Circulation Method

As reported previously (6,9), treatments with surfactant solutions were carried out dialy for four successive days on the inner surface of the forearm, where after treatment by the circulation method, the resulting skin response was clinically characterized by abnormal desquamation without any prior visible inflammation, referred to here as roughness. A clinical observation was made every day for 5 days by using the following standard based on degrees of desquamation. Marked scaling was denoted by ++, moderate scaling by +, and slight scaling by ±. Furthermore, cutaneous inflammatory reaction, if present, as indicated by redness and swelling of skin was judged by the evaluation criteria of closed patch test.

For statistical purposes roughness scores were given the following numerical values: 0 = no scaling (-), 0.5 = slight scaling (±), 1.0 = moderate scaling (+), and 2.0 = marked scaling (++). Similarly, the number of treatments necessary to produce the onset of roughness was given the following numerical values: 4.0 = one treatment, 3.0 = two treatments, 2.0 = three treatments, 1.0 = four treatments, and 0 = more than four treatments. Average skin roughness score was then calculated by dividing the sum of the numerical values given above by the total numbers of subjects. For example, when the number of persons having a + or ++ reaction brought on the first treatment were A and B, respectively, and the number of persons having first + reactions after four treatments were C, the average skin roughness score was calculated as 4.0 x 1.0 x A + 4.0 x 2.0 x B + 1.0 x 1.0 x C ÷ total numbers of subjects tested.

Closed Patch Test on Human Skin

All tests were performed as previously reported (9): 0.1 ml of surfactant solution was applied for 24 hr by the closed patch system on the inner surface of the forearm. The evaluation was carried out 2 hr or 24 hr after removal of the closed patch according to the following standard: - (negative): no reaction, ± (false positive): slight erythema, + (positive): erythema, 2+ (positive): erythema + edema, 3+ (positive): erythema + edema + serous papule. Irritation score was given following numerical values: 0 = 1, 0.5 = ±,

TABLE I

Physicochemical Properties of Monoalkyl Phosphate Sodium Salts with Various Alkyl Chain Lengths

Carbon number	Salt type	Krafft point (C)	CMC (mole/1)	pH at 1.0 g/100 ml (at 25 C)
10	Monosodium	20.0	---	5.3
	Disodium	20.0	---	10.7
12	Monosodium	31.5	3.5×10^{-3}[a]	6.0
	Sesquisodium	--	---	7.5
	Disodium	20.0	4.0×10^{-2}[b]	8.8
14	Monosodium	55.0	---	6.8
	Disodium	34.5	---	7.6
16	Monosodium	66.5	---	7.2
	Disodium	48.5	---	--
18	Disodium	62.0	---	---

[a]At 40 C.
[b]At 20 C.

TABLE II

Foaming Properties of Monoalkyl Phosphates Shown by Foam Height, Foam Stability, and Foam Density

	Concentration (mole/l)	Foam height (mm)	Foam stability (%)	Foam density (g/cm^3)
C_{10} MAP[a] mono Na	0.005	44	52.3	0.046
	0.01	112	85.7	0.098
	0.02	218	90.4	0.101
	0.05	213	91.5	0.075
C_{12} MAP mono Na	0.005	213	87.8	0.117
	0.01	231	84.8	0.139
	0.02	241	87.6	0.133
	0.05	231	85.7	0.147
C_{12} MAP di Na	0.005	0	---	---
	0.01	10	30.0	0.100
	0.02	167	38.3	0.120
	0.05	225	88.4	0.098
C_{14} MAP mono Na	0.005	195	86.2	0.139
	0.01	212	86.3	0.146
	0.02	194	83.0	0.124
	0.05	131	86.3	0.145
C_{14} MAP di Na	0.005	200	83.0	0.130
	0.01	223	87.0	0.135
	0.02	232	86.6	0.142
	0.05	207	91.8	0.121
C_{16} MAP mono Na	0.005	50	74.0	0.040
	0.01	48	58.3	0.042
	0.02	37	62.2	0.054
	0.05	42	97.6	0.095
C_{12} AS[b]	0.005	223	89.7	0.112
	0.01	207	91.3	0.082
	0.02	208	92.3	0.082
	0.05	208	91.3	0.077
C_{14} Soap[c]	0.005	249	85.1	0.161
	0.01	263	86.3	0.137
	0.02	255	86.7	0.142
	0.05	231	84.4	0.126

[a]MAP = monoalkyl phosphate.
[b]AS = alkyl sulfate.
[c]Soap = sodium carboxylate.

1.0 = +, 2.0 = 2+, 3.0 = 3 +. Average skin irritation score was then calculated by dividing the sum of the numerical values given above by the total numbers of subjects.

RESULTS AND DISCUSSION

Solubility and Krafft Point

It has been stated that although surfactants are precipitated as solids below their Krafft points, as the temperature is raised to their Krafft points, the aqueous solubility of surfactants increases markedly as a result of increasing dissolution of surfactant molecules in water due to the formation of micellar structures. Therefore, at the Krafft point the solution becomes transparent and its specific conductivity sharply increases. Krafft points of a series of MAP were thus determined from conductivity-temperature curves and are shown in Table I. Solubility-temperature curves of MAP mono- and disodium salts in aqueous solution are shown in Figure 2. Our results of measurements of solubility and Krafft point indicate that both mono- and disodium salts of C_{10} MAP can give clear water solutions at room temperature. On the other hand, C_{12} MAP monosodium salts with a Krafft point of 31.5 C were almost insoluble at room temperature, a behavior similar to that of C_{14} MAP disodium salts. In the case of the TEA salts, the ones with less than 14 carbon atom chain length were soluble at room temperature. Thus, in general, Krafft points of MAP monosodium salts are about 10-20 C higher than corresponding disodium salts, and the aqueous solubility of disodium salts is similar to that of analogous alkyl sulfates with the same carbon number.

In Figure 2, the solubility-temperature curves of MAP mono- and disodium salts show that the solubility curves shifted to higher temperature at the concentrations below 0.03 mole/1, at which concentrations these surfactants were insoluble even at temperatures higher than their Krafft points. Such a curious phenomenon has also been reported (12) for monoacylglutamates and is explained in the term of the hydrolysis of the surfactants. Thus, in our case also it is suggested that in dilute aqueous solution a part of MAP monosodium salts is hydrolyzed by way of bimolecular aggregates into corresponding disodium and unneutralized monoalkyl phosphate, and, as a result, the latter, due to its poor water solubility, precipitates, but at higher concentrations the precipitated unneutralized monoalkyl phosphates are solubilized by the dissolved MAP monosodium salts. In the case of MAP disodium salts, however, this phenomenon may be due to the presence of small amounts of unneutralized alkyl phosphate present as impurity.

CMC and Surface Tension

The break point in the specific conductivity vs. concentration diagram indicated that CMC was 3.5×10^{-3} mole/1 for C_{12} MAP monosodium salt and 4.0×10^{-2} mole/1 for its disodium salt. The latter value is in agreement with that reported by Tahara et al. (14). Although an aging effect of surface tension with time was observed with the mono- and disodium salts at low concentration, a minimum surface tension of C_{12} MAP monosodium salt was found to be 27.5 dyne/cm, which is near that of many anionic surfactants. C_{12} MAP disodium salt had a minimum surface tension of 39.5 dyne/cm. In addition, it appeared that the surface tension below the CMC was extremely lower. This may be due to adsorption of dissolved alkyl phosphoric acid present as impurity or their bimolecular aggregates onto interface.

TABLE III

Percent Oil Removal of MAP under the Conditions of 40 C, 10 min, or 30 min and 1300 rpm

	Concentration (g/100 ml)	Percent oil removal			
		1300 rpm, 10 min		1300 rpm, 30 min	
		Weight (%)	UV (%)	Weight (%)	UV (%)
C_{12} MAP[a] mono TEA	0.2	---	---	5.7	22.7
	0.5	7.7	17.8	31.9	48.8
	1.0	9.7	19.9	62.7	73.7
	3.0	31.6	51.6	---	---
C_{12} MAP mono Na	0.2	---	---	24.4	40.1
	0.5	---	11.4	32.3	49.7
	1.0	---	7.4	39.4	58.6
	3.0	0.4	23.3	---	---
C_{10} MAP mono Na	0.2	---	---	10.5	25.4
	0.5	2.5	11.8	28.1	39.8
	1.0	3.0	17.3	58.7	70.1
	3.0	14.2	22.6	---	---
C_{12} AS[b]	0.2	---	---	30.4	44.7
	0.5	2.3	18.5	42.3	56.0
	1.0	12.3	26.5	47.2	83.3
	3.0	38.3	51.4	---	---
Blank (water)		0.9	0	0	0

[a]MAP = monoalkyl phosphate.
[b]AS = alkyl sulfate.

Foaming Properties

Table II shows the effects of concentration on foaming properties at 40 C. Foam height and foam stability for each surfactant increased sharply as the concentration was raised from 0.002 to 0.01 mole/l and reached a plateau above a certain concentration. This concentration also corresponded to the CMC values of each surfactant. The minimum foam height seen for C_{16} MAP monosodium salt may be due to its insolubility, thus preventing micellar structure formation at this temperature. Furthermore, it can be seen that foaming power of the disodium salts was generally lower than that of the corresponding monosodium salts, and this is corroborated by the fact that the surface tension of the C_{12} MAP disodium salt was about 10 dyne/cm higher than that of its monosodium salt. Thus the foaming property data have revealed that at the concentrations above which micellar structure can be formed, MAP monosodium salts have as good a foaming power as do common anionic foaming agents such as alkyl sulfates. Further, the foam density values for these compounds are similar to C_{14} Soap, indicating that the foam produced by MAP monosodium salts is also creamy.

Defatting Potential

Table III shows defatting potential of the MAP in aqueous solution in comparison with C_{12} AS. Percent oil removal, as calculated on a weight basis, was less than that calculated by UV absorption, suggesting that there is preferential removal of dye or some adsorption of surfactant molecules into the remaining oil mixture. Our results indicate that MAPs at low concentrations of about 0.2% possess relatively low defatting potential, while at high concentrations of about 1.0% their defatting potential increases to as high a level as that for C_{12} AS, especially in C_{12} MAP mono-TEA salt.

Skin Toxicity

In vitro test (albumin optical rotation test): We have previously reported (8) that protein denaturing potency of surfactants can be evaluated by measuring specific rotation of bovine serum albumin in the presence of the surfactants, and that the potency data thus obtained correlate with the intensity of the skin roughness caused in vivo by the same surfactants. Table IV shows changes in specific rotation of bovine serum albumin at 0.2, 0.5, and 1.5 g/100 cml concentrations of MAP monosodium salts in comparison with various typical surfactants. For almost all anionic surfactants, the $[\alpha]_D$ values showed change in the following pattern. Initially, with the addition of a small amount of surfactants, the $[\alpha]_D$ value rapidly decreased in levorotation to a minimum, then gradually increased with increasing concentrations, and finally reached a plateau at a concentration of 1.0-1.5 g/100 ml. In contrast, the MAP monosodium salts showed that after an initial decrease in the $[\alpha]_D$ value, no increase toward levorotation was present even at higher concentrations.

As is clear from Table IV, typical anionic surfactants, C_{12} AS, C_{12} AOS and C_{14} SAS, which are known to have a marked roughening ability, show a greater increase of the $[\alpha]_D$ values toward levorotation, whereas all MAP monosodium salts have lower values, similar in pattern to those of nonionic surfactants such as C_{12}-14 EO with less roughening ability. Therefore, it is predicted that MAPs are as mildly roughening on the skin as nonionic surfactants.

In vivo tests: To confirm the results of the above in vitro test, skin-roughness tests were carried out in vivo by our circulation method (6,9) using C_{12} MAP monosodium and monoTEA salts and compared to C_{12} AS. With C_{12} AS, roughness was first induced in three out of ten subject. After one treatment with surfactant solution of 1.0 g/10 ml Concentration, the roughness intensity and number of subjects having roughness gradually increased during further applications, and on the fifth day a marked roughness was developed for half of ten subjects tested. On the other hand, with the MAP, roughness was scarcely observed during the 5 day test period, although a slight roughness was induced in one out of ten subjects after four treatments with C_{12} MAP monosodium salt.

A comparison of intensity of skin roughness for the MAPs and a variety of other surfactants (Table V) has revealed that surfactants such as C_{12} AS, C_{12} Soap C_{12} AOS and C_{12} LAS cause the most severe roughening, followed by C_{12}-3 ES, whereas C_{12}-14 EO produces less roughness. The MAPs, as expected, belong to the least roughening group out of all surfactants tested.

Table IV also shows the results for cutaneous reaction following a 24 hr closed patch test on the human forearm

TABLE IV

Cutaneous Effects of Monoalkyl Phosphates Shown by $[\alpha]_D$ Value, Roughness Score, and Irritation Score

Surfactants	$-[\alpha]_D$ 0.2[a]	$-[\alpha]_D$ 0.5[a]	$-[\alpha]_D$ 1.5[a]	Roughness score	n	Irritation score (n = 28) 4.0[a] 2 hr[b]	4.0[a] 24 hr[b]	2.0[a] 2 hr[b]	2.0[a] 24 hr[b]	1.0[a] 2 hr[b]
C_8 MAP mono Na	56.0	55.4	55.2	---		---	---	---	---	---
C_{10} MAP mono Na	56.6	57.3	56.8	---		0.31	0.30	0.02	0	---
C_{12} MAP mono Na	---	---	---	0.10	10	0	0	0	0	---
C_{12} MAP di Na	---	---	---	---		0.59	0.50	0.15	0.06	---
C_{12} MAP mono TEA	---	---	---	0	10	0	0	0	0	---
C_{14} MAP mono Na	---	---	---	---		0.17	0.07	0.19	0.04	---
C_{16} MAP mono Na	---	---	---	---		0	0	0.02	0.02	---
C_{18} MAP mono Na	54.7	57.4	---	---		---	---	---	---	---
C_{12} AS	57.4	62.7	65.1	3.06	36	---	---	---	---	1.19
C_{12} Soap	---	---	---	2.50	12	---	---	0.94	1.11	0.20
C_{12}-3 ES	55.3	61.1	63.0	0.46	12	---	---	0.26	0.19	---
C_{12} LAS	56.7	63.5	64.3	1.83	6	---	---	---	---	0.20
C_{12} AOS	55.5	57.9	64.5	4.75	4	---	---	---	---	0.23
C_{14} SAS	55.8	61.4	64.0	---		---	---	---	---	0.43
C_{12} AGS	---	58.4	58.1	---		0.07	0	0.09	0.04	---
C_{12}-14 EO	57.0	57.0	57.3	0	12	0.02	0	0.02	0	---

[a]g/100 ml MAP = monoalkyl phosphate; AS = alkyl sulfate; Soap = sodium carboxylate; LAS = alkyl benzene sulfonate; ES = alkyl polyoxyethylene sulfate; AOS = alfa olefin sulfonate; SAS = paraffin sulfonate; AGS = monoalkyl acylglytamate; EO = alkyl polyoxyethylene.
[b]Hours after removal of patch.

at 1.0, 2.0, and 4.0 g/100 ml concentrations of various surfactants including MAPs. Although the MAPs produced varying degrees of irritation depending on alkyl chain length or salt type, two typical types of MAP, C_{12} MAP monosodium and mono TEA salts, gave no cutaneous reaction at 2.0 and 4.0 g/100 ml concentrations. This finding suggests that the irritation potential of such MAPs is less than that of C_{12} AGS and also as low as that of nonionic surfactants. By contrast, C_{12} MAP disodium salt and C_{10} MAP monosodium salt showed an irritancy greater than that of C_{12} AGS. On the basis of the findings described above, it is concluded that, in general, MAP has a very low irritation potential as compared to C_{12} AS or even C_{12} Soap.

AS, LAS, AOS, and ES have been employed as surfactants for household uses because such surfactants have good foaming properties and detergency. However, it has been pointed out (1,2,4,6) that these surfactants also produce greater skin damage than other varieties of surfactants. This means that repeated exposures of the skin to such surfactant solution may invoke skin roughness and /or skin irritation. In fact, in dishwashing, where direct and repeated contact of skin with surfactant solutions occurs, hand roughness has increased recently.

In order to devise surfactants combining both low skin irritation and good detergency we have investigated (5,8,10) factors influencing skin irritation inducing effect of surfactants. These studies have established (7) that there is a relation between chemical structure of a surfactant, such as alkyl chain length and polar terminal group, and potential for skin irritation. Such effects can be described as follows: (a) with respect to the polar group, irritation decreases in the order of OSO_3^-, SO_3^-, benzene-SO_3^- and COO^-; (b) irritation decreases in the order of C_{12}, C_{10}, C_{14}, C_{16}, C_8, and C_{18} of the alkyl chain length; (c) the larger the surfactant molecular weight, the lower the potential for irritation. In MAP, a terminal group of SO_3^- or OSO_3^-, usually found in anionic surfactants was replaced by OPO_3^- to enhance safety on human skin.

The CMC value and surface tension of typical MAP, C_{12} MAP monosodium salt was 3.5×10^{-3} mole/l and 27.5 dyne/cm, respectively; thus surface-active properties were similar to those of common anionic surfactants. As to their foaming properties, a compound (C_{12} MAP monosodium salt) gave even a higher foam than C_{12} AS, and its foam density was very close to that of soap. The defatting potential was similar to that of C_{12} AS and thus adequate for washing. With respect to skin damage, MAPs demonstrated high safety in comparison with a variety of surfactants used commonly in household products; as shown by our circulation method and closed patch test, they had skin roughening and irritating effects similar to those of general nonionic surfactants such as C_{12}-14 EO. Thus MAP makes a good and a safe detergent. In the past, it has been assumed that surfactants with good surface-active properties also exhibit a marked potential for damaging the skin, however, MAPs have low roughening and irritating characteristics despite their good surface-active properties.

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