

SURFACE ACTIVE AGENTS: CHEMICAL TYPES AND APPLICATIONS¹

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The rapid growth of the chemical industry in this country has greatly increased the number of new chemicals whose physiological effects must be reckoned with. Thus, the armamentarium of the dermatologist has been considerably strengthened by the addition of numerous synthetic products, the so-called surface active agents (1). It is the purpose of this review to describe the chemical type and classification of these synthetic organic products, and to give some examples of their use in the compounding and administration of therapeutic agents.

I. CHEMICAL TYPES

Although the terms "wetting agent" and "synthetic detergent" have been used almost synonymously to describe the synthetic organic products used for wetting, penetrating, emulsifying, dispersing, solubilizing, foaming and washing, it is convenient to call such products generally "surface active agents." Some uses, such as detergency, may require wetting and penetrating power to wet a soiled surface, solubilizing power to dissolve oils or greases, dispersing and suspending power to hold insoluble particles and prevent redeposition, and foaming ability for the sake of appearances. Other uses may require only a simple wetting action. Whereas good detergents usually have good wetting powers, some excellent wetting agents are poor detergents, and some good emulsifiers are indifferent wetting agents.

Foaming agents make possible a temporarily stable mixture of air with a liquid. Emulsifiers stabilize the dispersion of a liquid within a liquid, making possible emulsion creams or ointments of oil and water which spread readily in a thin continuous layer on clean or oily skin (2). In many cases the same surface active agent may be used for several different purposes.

The surface active agents have the general property of lowering surface or interfacial tension of liquids, an effect which may be measured quantitatively in artificially purified systems. In practice, the correlation between the behavior of surface active materials in purified systems and in the complex lipid-aqueous systems of the body is by no means good, and surface-tension lowering is not a reliable criterion of effectiveness.

In a practical sense, these surface-active agents function by promoting contact, mingling, or wetting, between two ordinarily incompatible materials, such as oil and water. This effect is achieved by combining, in the molecule of a surface-active agent, a water-seeking or *hydrophilic* portion, and an oil-seeking *lipophilic*, or *hydrophobic* portion. Roughly speaking, one part of the molecule dissolves in the oil or lipid phase, the other in the aqueous phase, and thus

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“ties” the two ordinarily immiscible phases together. Since only the surfaces of the two phases are involved, and since surface-active materials always concentrate at the interfacial surface, comparatively small amounts on the order of 0.1 to 1.0% are often sufficient.

The hydrophilic portion may be either ionic or nonionic. The ionic group is usually in the form of a salt, wherein either the acid (anionic) or base (cationic) part of a salt, is attached to the lipophilic group. Such ions include —COO^- (carboxylate), $\text{—OSO}_2\text{O}^-$ (sulfate), $\text{—SO}_2\text{O}^-$ (sulfonate), and $[\text{—N}(\text{CH}_3)_3]^+$ (quaternary ammonium). The nonionic residues are either polyhydroxylic (glycerol, sorbitol, glucoside), or polyoxyethylene $\text{—O}[\text{CH}_2\text{CH}_2\text{O}]_n\text{CH}_2\text{CH}_2\text{OH}$.

The hydrophobic, or lipophilic portion is hydrocarbon in character, and may be either the long straight aliphatic carbon chain found in the natural fats, the straight, branched, or cyclic saturated hydrocarbons of petroleum, or aromatic hydrocarbons (benzene, naphthalene) containing alkyl side chains (3).

The *common soaps* have the hydrophilic carboxylate ion—usually as sodium or potassium salt—at the end of a long lipophilic hydrocarbon chain.

$\text{CH}_3(\text{CH}_2)_{10}\text{COO}^-\text{Na}^+$ = sodium laurate—a good foaming agent

$\text{CH}_3(\text{CH}_2)_7\text{CH}=\text{CH}\cdot(\text{CH}_2)_7\cdot\text{COO}^-\text{Na}^+$ = sodium oleate—a good emulsifier

$\text{CH}_3(\text{CH}_2)_{16}\text{COO}^-\text{Na}^+$ = sodium stearate—a good *hot water* detergent

The soaps are insoluble in acid solution, and are likewise precipitated by the calcium ion of hard water, or the magnesium in sea water.


The *fatty alcohol sulfates* have a terminal $\text{—OSO}_2\text{ONa}$ instead of —COONa of a soap. The sulfate group is more hydrophilic than the carboxylate.

$\text{CH}_3(\text{CH}_2)_{10}\text{CH}_2\text{OSO}_2\text{ONa}$ = *sodium lauryl sulfate*—a good hard-water detergent

Since their calcium and magnesium salts are readily water soluble, these long-chain alkyl sulfates can be used in hard water or sea water. The allyl sulfates are hydrolyzed by boiling dilute acids.

More stable are the *sulfonates of alkylated benzene or naphthalene*, where the sulfonic group is attached by a stable C—S linkage to the aromatic nucleus.

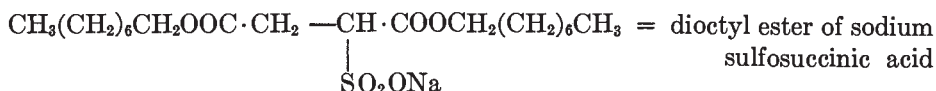
Alkyl  $\text{SO}_2\text{O}^-\text{Na}^+$ = alkyl aryl sulfonate—wetting agent, detergent.

$\text{CH}_3(\text{CH}_2)_{15}$  = cetyl pyridinium chloride—an acid stable, “cationic soap”
N⁺Cl⁻

In the preceding types, the hydrophilic group has been at one end of the molecule. It is likewise possible to put the hydrophilic group in the middle of a hydrophobe chain—or between two similar lipophile groups. Treatment of fatty oils with sulfuric acid gives a mixture of mid-chain sulfate and sulfonate,

the so-called turkey red oils, which were the first synthetic, acid-stable surface active agents, used in dyeing.

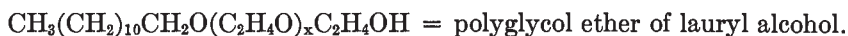
An *ester sulfonate* is exemplified by:



This is one of the most effective wetting agents. Shorter-chain homologs such as the diamyl and dibutyl esters are likewise used.

It is evident that, by using one or more hydrocarbon chains of different lengths, the balance between hydrophile and hydrophobe character can be shifted, and the compound as a whole can be rendered oil-soluble or water-soluble.

Nonionic surface active agents are exemplified by the *mono esters of sorbitol anhydrides*, and by



The polyglycol chains can likewise be attached to the free hydroxyls of a monoester of a polyhydric alcohol ether.

The following classification of the commoner, established materials is based on that of Wilkes and Wicker (4), as modified by Caryl and Ericks (5) and the writer.

R = long chain paraffinic or olefinic group—usually C₁₂ to C₂₂.

R' = primary or secondary, straight or branched-chain lower alkyl group—usually C₄ to C₁₀.

A = anion—Cl, Br, I, HSO₄.

Ar = Aryl group—phenyl, naphthyl, diphenyl, etc.

M = Alkali metal, ammonium or substituted ammonium, e.g., Na, K, triethanolamine.

By ringing the changes on the industrially available hydrocarbons, fatty acids, alcohols, nitrogen bases, and inorganic oxyacids, a large number of useful products may be and have been elaborated. Beeler (6), Cupples (7), and Van Antwerpen (8) have prepared lists containing nearly 300 commercial products. Adam (9), Snell (10), Fischer (12) and others have discussed their chemical types and structures (when revealed) in detail. The following list contains only a few of the better known products.

The so-called nonionic agents in Group D are not as widely known as those of Groups A, B, and C. Strictly speaking, the hydroxyls of types 1 and 2 in Group D could be considered as very weak acids, and the ether oxygens of Types 3, 4 and 5 as oxonium or cationic residues, but, in comparison with the typical strongly ionic members of Groups A, B & C they may be looked upon as non-

ionic. They are virtually lacking in toxicity, and irritating effect on the skin. Several of the newer materials are being used extensively in military pharmaceuticals.

TABLE I
Chemical classification of surface active agents

GROUP	FORMULA OF TYPICAL REPRESENTATIVE	TYPE	TYPE DESCRIPTION
A	Anionic—Terminal Hydrophile Group		
	RCOOM	1	Soap
	ROSO ₂ OM	2	Fatty Alcohol Sulfate
	RCONHC ₂ H ₄ OSO ₂ OM	3	Sulfated Hydroxyethyl Amide
	RCOOC ₂ H ₄ OSO ₂ OM	4	Sulfated Fatty Acid Partial Ester
	RCH ₂ OOCCH ₂ SO ₂ OM	5	Fatty Alcohol Sulfoacetate
B	Anionic—Central Hydrophile Group		
	(R') ₂ CHOSO ₂ OM	1	Sulfated Secondary Alcohol
	R'CHR'	2	Sulfonated Hydrocarbon
	$\begin{array}{c} \\ \text{SO}_2\text{OM} \\ \text{R}_2\text{ArSO}_2\text{OM} \\ \text{R}'\text{OOCCH}_2\text{CHCOOR}' \\ \\ \text{SO}_2\text{OM} \end{array}$	3	Alkyl Aryl Sulfonate
4	Sulfonated Ester of Alcohols and Dibasic Acids		
C	Cationic—Usually Terminal Hydrophile Group		
	[RN(CH ₃) ₃] ⁺ A ⁻	1	Long-chain Quaternary Ammonium Salt
	[R—Pyridine] ⁺ A ⁻	2	Alkyl Tertiary Aryl Ammonium Salt
D	Nonionic		
	RCOOC ₃ H ₅ (OH) ₂	1	Polyhydric Alcohol Partial Fatty Acid Ester
	RCOOC ₆ H ₅ O(OH) ₂	2	Anhydro Polyhydric Alcohol Partial Ester
	RCH ₂ O(C ₂ H ₄ O) _n C ₂ H ₄ OH	3	Fatty Alcohol Polyoxyethylene Ether
	RCOOC ₆ H ₅ O[(C ₂ H ₄ O) _n C ₂ H ₄ OH] ₂	4	Polyoxyalkylated Anhydro Polyhydric Alcohol Fatty Acid Ester
	RArO(C ₂ H ₄ O) _n C ₂ H ₄ OH	5	Alkyl Phenol Polyoxyethylene Ether
E	Miscellaneous		Hydrophobe-hydrophile Phosphates, Phosphonates, and Borates

Types 1 and 2, as partial fatty acid esters of polyhydric alcohols, are closely related chemically to the natural fats. These surface active compounds are still oil-soluble, since the hydroxyl groups are not numerous enough to impart water

TABLE II
Commercial products

	SUPPLIER'S DESCRIPTION	TYPE	SUPPLIER
Group A			
Artic Syntex A.....	Sulfonated fatty ester	4	Colgate-Palmolive-Peet Co.
Duponols.....	Alkyl sulfates	2	DuPont Co.
Gardinols.....	Sodium alkyl sulfates	2	DuPont Co., Procter & Gamble
Igepon T.....	Condensation product of fatty acid with amino sulfonic acid	3	General Dyestuff Corp.
Nacconol LAL.....	Sodium lauryl sulfoacetate	5	National Aniline & Chem. Corp.
NOPCO 1086-B.....	Short chain aliphatic ester sulfonate	5	National Oil Product Co.
Orvus WA.....	Sodium Salt or technical lauryl sulfate	2	Procter & Gamble
Sulfanole.....	Sulfonated fatty acid amide		Warwick Chem. Co.
Group B			
Aerosol OT.....	Di-octyl sodium sulfosuccinate	4	Amer. Cynamid & Chem. Corp.
Alkanols B, SA.....	Sodium alkyl naphthalene sulfonate	3	DuPont Co.
HG			
S	Sodium tetrahydronaphthalene sulfonate	3	“ “
WXN	Sodium hydrocarbon sulfonate	2	“ “
Areskap.....	Monobutyl phenyl phenol sodium monosulfate	3	Monsanto Chem. Co.
Beaconol A.....	Monoethyl phenyl phenol sodium monosulfate	3	Beacon Co.
Invadines.....	Alkyl phenylene sodium sulfonate	3	Ciba Co., Inc.
Lanitol.....	Sodium alkyl aryl sulfonate	3	Arkansas Co.
Nacconols E, NR.....	Sodium alkyl aryl sulfonate	3	National Aniline & Chem. Corp.
Santomerse.....	Alkylated aryl sulfonate	3	Monsanto Chem. Co.
Sulfatate.....	Sodium salt of sulfonated hydrocarbons	2	Glyco Products Co.
Tergitols.....	Triethanolamine derivatives of 7-ethyl-2-methyl-4-undecanol (alkyl sulfates)	2	Carbide & Carbon Chem. Corp.
Group C			
Beta Sol.....	Quaternary ammonium salt	?	Onyx Oil & Chem. Co.
Cationic Agents C, D.	Substituted amide of alkyl phosphate (12 and 18 carbon)	?	Victor Chem. Wks.
Negamine.....	Cation-active amino esters of long-chain fatty acids	1	Synthetic Chem. Inc.
Triton K-60.....	Cetyl dimethyl benzyl ammonium chloride	1	Rohm & Haas Co.

TABLE II—*Concluded*

	SUPPLIER'S DESCRIPTION	TYPE	SUPPLIER
Group D			
Arlacel B, C.....	Anhydrohexitol partial oleats	2	Atlas Powder Co.
Diglycol Laurate S...	Lauric Acid ester of diethylene glycol	2	Glyco Prod. Co.
Intrals 222, 231.....	Polyethers	3 (?)	Synthetic Chem. Inc.
Pentamul 6.....	Pentaerythritol monostearate	1	Heyden Chem. Corp.
Spans.....	Sorbitan fatty acid partial esters	2	Atlas Powder Co.
Triton NE.....	Aryl alkyl polyether alcohol	5	Rohm & Haas Co.
Tweens.....	Polyoxyalkylated soritan fatty acid esters	4	Atlas Powder Co.

solubility to the composition as a whole. In Type 3, the hydrophile portion of the partial esters has been amplified by the addition of the polyoxyethylene chains, or polyglycol ethers, whose solubilizing groups is $-\text{OCH}_2\text{CH}_2$.

The *oxyethylene* group is a *weaker hydrophile* than the *hydroxyl*, but a sufficient number of them will drag any hydrocarbon residue into aqueous solution. For the commoner fatty acid radicals, C_{12} to C_{20} , from 10 to 20 oxyethylene groups are required. As the oxyethylene groups increase, oil compatibility is likewise diminished. Hence a continuous transition from oil to water solubility is readily obtainable with this nonionic type, by varying the hydrocarbon chain length and the amount of polyoxyethylene. The hydrophile portion of these nonionic compounds is thus very much larger than the ionic group in the other classes. The water soluble Carbowaxes 1500 and 4000 are polyglycols having polyoxyethylene chains averaging 35 and 90 units, respectively.

Combinations of Types 2 and 4 in the nonionic group are often used, particularly for emulsification. The nonionic groups are compatible to some degree with both anionic and cationic types.

The agents of groups *A*, *B* & *C* are primarily *penetrating* agents, while the nonionic *group D* tend to act as *spreaders*, rather than penetrants. Many products in *A*, *B* and *D* are *good detergents*—the sodium alkyl aryl sulfonates of *B* are particularly effective. The *D group* are primarily *emulsifiers*. Dispersing efficiency is difficult to classify.

No hard and fast rules for correlating uses with chemical structures are known, though many have been attempted. Quite frequently the same agent is employed for several purposes. The greatest interest therefore attaches to examples of practical applications.

II. APPLICATIONS

A detailed discussion of applications, or of reasons for choosing one surface active agent in preference to another, is too lengthy for the purpose of this article, but certain properties and needs can serve as guideposts. For example, the solubility of the emulsifier and its stability in the presence of the desired medicament is a matter of prime importance. An emulsifier that is *primarily*

oil-soluble tends to produce *water-in-oil* (W/O) type emulsions. A *water-soluble surface active agent* will produce *oil-in-water* (O/W) type emulsions. Combinations of mutually compatible emulsifiers generally give more stable emulsions. Water-soluble agents are essentially "wetting-out agents," finding major usage in textile operations, in detergency, etc. Oil-soluble agents seem to give more tenacious films, promoting emulsion stability and water holding powers so that they are widely used alone or in combination with the water soluble agents as emulsifiers, dispersing agents and insecticide spreaders.

Many of these products have been used repeatedly and for long periods as soap substitutes and as ingredients in dermatologic ointments (1, 15, 23). Some have been used in foods and medicinal syrups. However, it is always wise to consider the available background data when approaching new applications.

Ointment Formulations

Emulsified ointment bases, whether of the O/W or W/O type have several advantages for topical applications. Keratolytic effects occur more rapidly, the zone of inhibition of bactericidal agents increases; the ointments spread more readily; medicaments are liberated more rapidly from grease bases; and insolubility problems can frequently be overcome.

Until relatively recently most standard ointments have been prepared by mixing medicaments with simple oils, hydrous wool fat, lard or petrolatum. If the substance to be added is a powder or a material insoluble in the ointment base, it requires careful technique to insure even distribution of the medicament throughout the base.

The literature of the past few years has many reports on the work of the various investigators on the formulation, and on the clinical value of new forms of ointments that contain water. These emulsion-type ointments allow the medicament to be dissolved or dispersed in either the oil or water phase (11, 12, 13, 14). Thus a more uniform distribution of the active ingredient is assured, while difficulties of incorporation are greatly decreased.

By using the proper emulsifier, either *water-in-oil* (W/O) or *oil-in-water* (O/W) type emulsions can be produced. The following formulas will serve to illustrate both types of emulsions (15). They all have shown good stability in the presence of a number of typical medicaments, such as zinc oxide, salicylic acid, boric acid and calomel.

<i>Formula</i>	<i>No. 1</i>	<i>No. 2</i>	<i>No. 3</i>
Arlacel A or C.....	4.5	5.0	4
Beeswax (white).....	2.25	—	—
Ceresine Wax.....	—	5.0	2
Lanolin (anhyd.).....	—	10.0	—
Petrolatum.....	27.0	7.5	24
Mineral Oil.....	11.25	22.5	10
Medicament.....	10.0	10.0	20
Water.....	45.0	40.0	40

Preparation: Melt and hand stir the mixed oils and waxes at about 70°C. Add the heated water solution of the medicaments and stir until the temperature drops to 40°C.

<i>Formula No 23</i>		Preparation:
1. Spermaceti.....	10%	
2. Tween 61.....	12%	added to (4 + 5 at 85°C.)
3. Zinc Oxide.....	15%	Stir to 40°C.
4. Water.....	63%	
5. Preservative.....	q.s.	

Formulas 1, 2 and 3 are W/O type, while No. 23 is an O/W (washable) type ointment.

Duemling has tested a large number of ointments, many of which have been suggested as a result of his cooperative work with Powers of the N.F. Committee and the American Pharmaceutical Association Laboratories (13). Three of these washable ointment bases are listed below:

<i>Formula</i>	<i>No. 4</i>	<i>No. 5</i>	<i>No. 7</i>
Sodium Lauryl Sulfate.....	0.5	1.5	1.0
Hexadecyl (Cetyl) Alcohol.....	8.0	6.4	1.5
Octadecyl Alcohol (Stenol).....	—	6.4	5.0
Cocoa Butter.....	6.5	—	—
White Petrolatum.....	20.0	14.3	—
Liquid Petrolatum.....	—	21.4	15.0
Spermaceti.....	—	—	20.0
Paraffin.....	—	—	10.0
Water.....	65.0	50.0	47.5

Ointment No. 4 is the Gibson base (16); No. 4 described by Mumford (17) is the University of Chicago Hospital base; No. 7 is a commercial product described by Duemling (1). All are washable bases, akin to the vanishing creams used in cosmetics.

The choice of proper base for ointment usage is governed by several factors (11). It should cling to the skin, possess a certain amount of stickiness and spread rather easily. No one base is the best for all antiseptic drugs. Ability to penetrate the epiderm is sometimes desirable, but is not necessarily an indication of superiority. For endermic absorption each drug offers a separate problem. Many investigators have therefore recommended bases that differ widely in the effects obtained.

The so-called "penetrasols" of Hermann, Sulzberger and Baer (22) are a new type of compounded vehicle, designed to increase percutaneous absorption by combining the properties of fat or lipid solubility, water solubility, surface-wetting action, and solvent power. An example is a mixture of xylene or derivative thereof, a "synthetic wetting agent," and propylene glycol. These are marketed under the name "*Intraderm*". Experiments have been reported which demonstrated that these compositions accelerate the penetration of a great variety of substances through grossly intact human and animal skins (sulfonamides, heavy metals, so-called protein allergens, etc.).

Washable ointment bases (i.e., O/W type emulsions) are favored by many workers because they can be easily washed from the skin with water, little or

no friction being required. However, the W/O type emulsion ointment, in which the water phase is surrounded by non-volatile oily materials, does not dry out as rapidly, possesses enhanced emollient properties and is often less irritating. Both types appear to have many advantages over non-emulsion ointments.

The type of base is important when using bacteriostatic medicaments (e.g. the sulfonamides) incorporated in a bland grease base. To obtain appreciable diffusion of sulfathiazole, for example, from a petrolatum base, it is necessary to add some type of surface active agents to the ointment base. This has been shown by the work of Pillsbury and his co-workers (18, 19), the Robinsons, Price, Combes and Canizares, Keeney et al. (20), Jenkins and his associates (21) and many others. The sulfathiazole may be incorporated in petrolatum alone, or in either a W/O or O/W emulsion base.

<i>Formula</i>	<i>No. 15</i>
Sodium Lauryl Sulfate.....	1.0%
Stearyl Alcohol.....	10.0%
Cetyl Alcohol.....	3.0%
Spermaceti.....	10.0%
Glycerine.....	10.0%
Sulfathiazole.....	5.0%
Water.....	61.0%

<i>Formula</i>	<i>No. 16</i>
Petrolatum.....	48 cc.
Arlacel C.....	2 cc.
Sulfathiazole.....	5 gm.
Tween 80.....	½ cc.
Water q.sa.d.....	100 cc.

Formula No. 15 is the oil-in-water type emulsion base used by Pillsbury et al. (18, 19), while Formula No. 16 is the water-in-oil type base developed by Jenkins et al. (21). Both bases can be readily prepared, requiring no special techniques.

Protective Ointments

“The keynote of the prevention of occupational dermatitis is to keep contact of irritants with the skin at a minimum.” Since all protective ointments should be easily applied and easily removable after use, the need for surface active agents is evident. Schwartz (23) has published an excellent article on this subject, listing formulas, types and suppliers of both ointments and surface active agents that were widely available before the war.

Detergents

It is desirable to use water instead of an organic solvent in removing oils, greases and dirt from the body. Many investigators are today of the opinion that *vigorous cleansing methods* or the use of potentially *tissue damaging solvents* are *contraindicated in the preliminary treatment* of burns and open wounds or of acutely inflamed dermatoses. The value of synthetic detergents lies in their

ability to penetrate and solubilize substances such as greases, oils, and fats, as well as particulate matter. These types of contaminants are thus rendered more easily removable by water.

In choosing the detergents to be used, lack of skin irritating properties is obviously more important than ability to produce copious foam. Fairly high oil solubility is also generally necessary, in order to avoid the use of much mechanical pressure and friction in application to sensitive skin. Rosenberg (24) relied on the use of a penetrant detergent as a carrier for other more powerful detergents. Jenkins and his associates (21) have suggested using 5% Tween 80 in a physiological saline solution for use on burned surfaces. The use of green soap and water is of course well known, but the use of synthetic detergents as soap substitutes and as ingredients in dermatologic ointments has certain distinct advantages and is increasing rapidly.

A typical formula suggested by Schwartz (23) is the following cleanser (a solid cake form):

Nacconol (or Santomerse, Igepon or Duponol).....	20
Lanolin.....	3
Colloidal Clay.....	76
Perfume.....	1

This was apparently developed especially for soap-sensitive workers. However, it should be noted that skins may be allergic not only to soaps but to various surface active agents other than soaps.

Miscellaneous Applications

Surface active agents are often used to *solubilize* water insoluble materials, —such as the oil soluble vitamins. They are used to *promote lotion stability*. They permit extremely *high dilutions* of highly active, as well as of highly toxic, substances, promoting *even dispersion over a wide area*.

Examples: 1) the oil-soluble and water-soluble vitamins can be simultaneously administered in an aqueous vehicle.

2) The appearance and evenness of spreading of calamine lotions can be improved.

3) Preparations containing DDT (or other insecticides or insect repellents) can be diluted with water for washing or spraying in delousing humans or destroying mosquitoes or protecting objects, fabrics and persons. 4) Surface active agents are used in softening of leather, in the laundry industry, in almost all methods of textile treatment, in paints, disinfectants, adhesives and in the cosmetic and food industries. The applications are almost limitless (25, 26, 27, 28, 29, 30).

III. POSSIBLE FUTURE TRENDS

No radically new chemical types of surface active agents have appeared in the last decade. Although chemical innovation is by no means improbable, it is more likely that the main lines of development in surface active substances will

be in the direction of a better understanding of the underlying theory of their behavior, a large increase in knowledge of specific applications, the discovery of synergistic combinations of medicaments and surface active adjuvants, and a more complete picture of their physiological action. Although many of the most useful products are complex mixtures, much of the systematic research will probably be done on pure chemical compounds.

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