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Journal of the Society of Cosmetic Chemists

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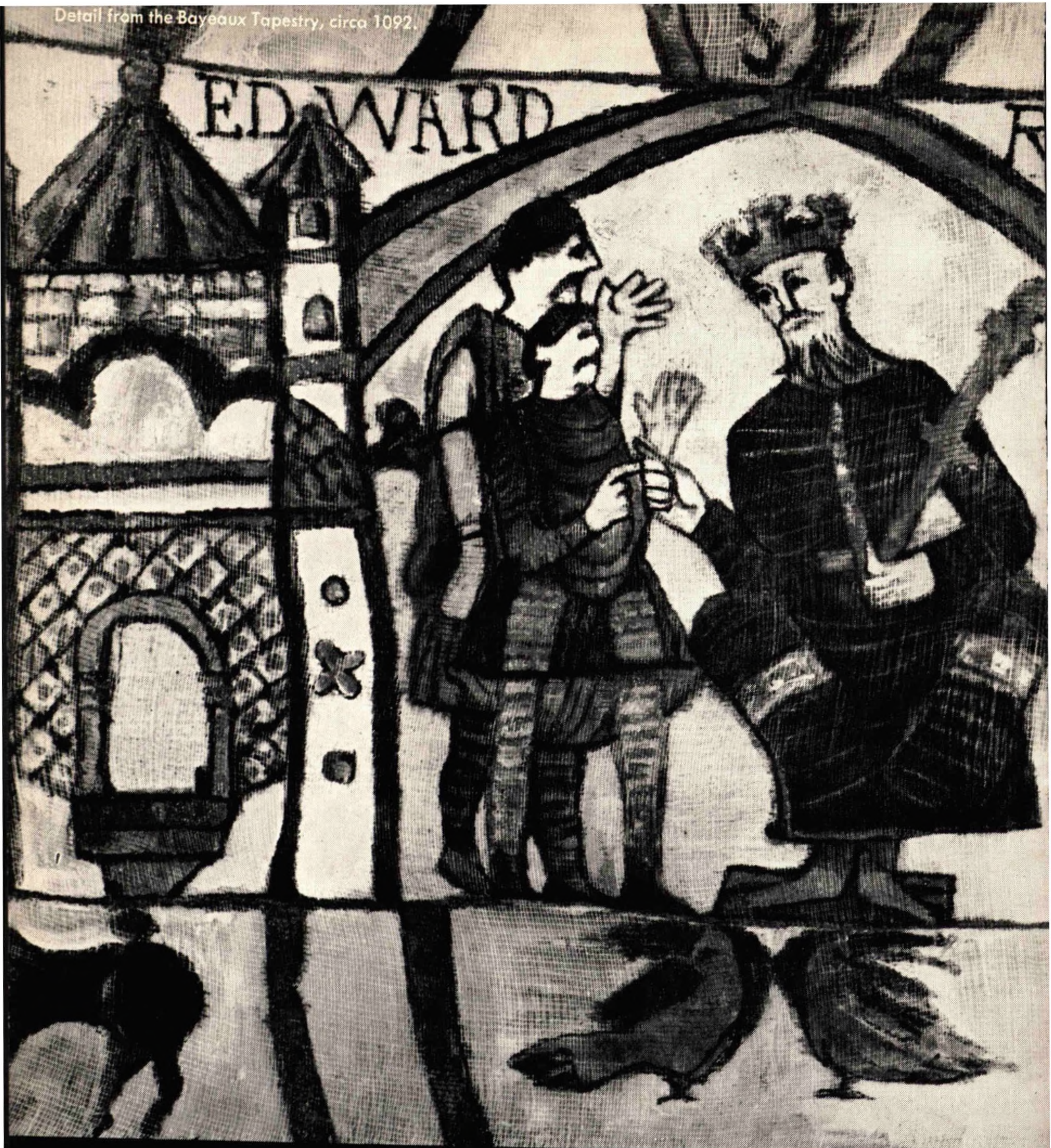

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Journal of the Society of Cosmetic Chemists

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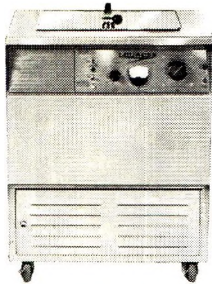

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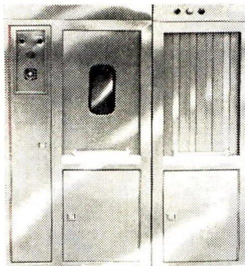

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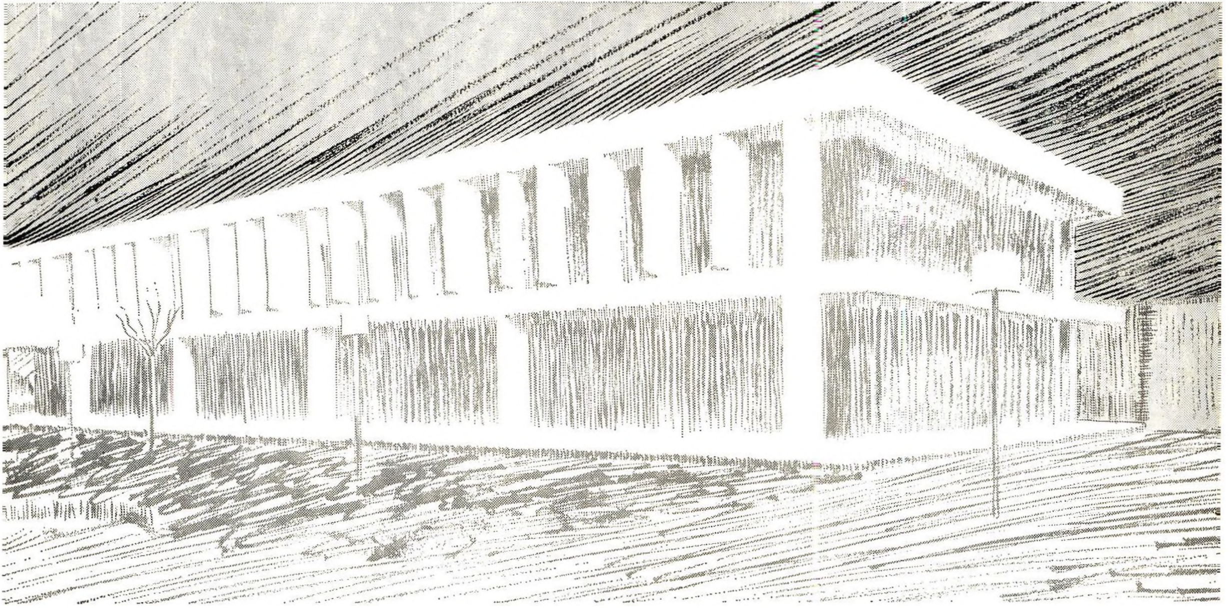

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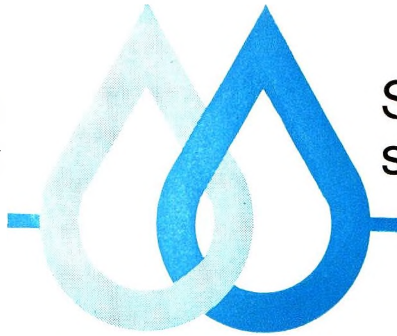

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Identification of preservatives in cosmetic products by thin-layer chromatography: Clifton H. Wilson. *Journal of the Society of Cosmetic Chemists* **26**, 75 (February 1975)

Synopsis—A rapid, sensitive method for the identification of preservatives in cosmetics consists of extracting the cosmetic with alcohol and developing an aliquot of the extract on a thin-layer chromatography (tlc) plate of silica gel GF_{254}. The preservatives are visualized on the plate by short wavelength UV light, iodine vapor, and/or several indicator sprays, and identified by comparison of R_f values with known standards. Twenty-five preservatives were characterized by this method. The preservatives in nine commercial cosmetic products were identified by the method described. The limit of detectability is approximately 0.1–0.5 μg on a tlc plate, using a benzene-acetone solvent system.

Aerobic microflora of the outer eye area of women of Los Angeles, Calif.: John F. McConville and David W. Anderson, Jr. *Journal of the Society of Cosmetic Chemists* **26**, 83 (February)

Synopsis—Several reports have enumerated the microflora of used eye cosmetics. However, there is a paucity of literature describing the microflora of the outer eye area. Understanding of the microflora of the outer skin around the eye should be useful in the development of preservative systems for eye cosmetics. The purpose of this paper is to contribute to the knowledge of the microflora of the outer eye as determined in selected subjects residing in Los Angeles, Calif.

The absorption potential of skin: F. Meyer and J. Ziegenmeyer. *Journal of the Society of Cosmetic Chemists* **26**, 93 (February **1975**)

Synopsis—Penetrants are defined as materials which can transport actives into the corium of skin and act as accelerators of absorption. Transport into the corium appears to occur in toto without any appreciable selectivity. Within the epidermis the penetrant evidently loses its efficacy, and transport becomes increasingly dependent on the active. The velocity of percutaneous absorption can be exceedingly high. Thus the presence of dyes in the corium or the action of lidocaine can be demonstrated already 15 minutes after external application. Differences in absorption between laboratory animals and man can be expected and are related, in part, to the thickness of the epidermis and the density of hair. Finally, it has been known for some time that diseased, damaged, or aged skin has an altered ability to absorb foreign materials. The behavior in the skin will, of course, have a major influence on capillary absorption. Depot action in the epithelium must also be considered since resorption can continue even after termination of external contact. This appears particularly important in the case of cosmetics since, in principle, acceleration of penetration is possible. Sometimes, this is desirable for an intentional "deep" action. Often, it will however be less desirable because the unavoidable absorption cannot be controlled. It is not certain whether and to what degree penetrants or the subsequent interference with penetration can be used to generate meaningful effects in deeper layers of the skin. In principle it appears at least theoretically possible to control the depth of penetration. On the other hand, it is frequently methodologically extremely difficult to describe the required parameters quantitatively. Overall, the technological efforts of cosmetic research should be supported more than previously by animal experimentation. This will permit an early determination whether percutaneous absorption of materials from cosmetic preparations can occur or can be precluded.

The influence of pH, emulsifier, and accelerated ageing upon preservative requirements of O/W emulsions: Gene Jacobs, S. M. Henry, and V. F. Cotty. *Journal of the Society of Cosmetic Chemists* **26**, 105 (February 1975)

Synopsis—Twenty-nine individual preservatives and 16 combinations of two or more preservatives were tested in an anionic and a nonionic oil/water lotion, each of which was formulated at an acid and an alkaline pH. Minimum inhibitory concentrations against four representative challenge microorganisms were determined for the preservatives and/or combinations. Less than 35% of the preservatives or systems tested in lotions were effective. Anionic emulsions were somewhat easier to preserve than formulas made with nonionic emulsifiers.

J. Soc. Cosmet. Chem., **26**, 75–81 (February 1975)

Identification of Preservatives in Cosmetic Products by Thin-layer Chromatography

CLIFTON H. WILSON, Ph.D*

Synopsis—A rapid, sensitive method for the IDENTIFICATION of PRESERVATIVES in COSMETICS consists of extracting the cosmetic with alcohol and developing an aliquot of the extract on a THIN-LAYER CHROMATOGRAPHY (tlc) plate of silica gel GF_{254}. The preservatives are visualized on the plate by short wavelength UV light, iodine vapor, and/or several indicator sprays, and identified by comparison of R_f values with known standards. Twenty-five preservatives were characterized by this method. The preservatives in nine commercial cosmetic products were identified by the method described. The limit of detectability is approximately 0.1–0.5 μg on a tlc plate, using a benzene-acetone solvent system.

Introduction

Chemicals with preservative properties are widely used in cosmetic products. These chemicals include halogenated phenols, hydroxybenzoates, formaldehyde-releasing compounds, and a few heterocyclic compounds such as dehydroacetic acid. Most of these compounds absorb in the ultraviolet region of the spectrum. Derry *et al.* (1) published a method for detecting several preservatives in cosmetics with a detectability limit of 0.1%. The method involves separation by extraction and partition chromatography followed by spectrophotometric examination. Many preservatives, however, are used at concentrations of less than 0.1% and therefore could not be detected by this method.

The present study was undertaken to develop a rapid screening procedure to identify preservatives in cosmetic products at levels below 0.01%.

*Division of Cosmetics Technology, Food and Drug Administration, 200 C Street, S.W., Washington, D.C. 20204.

Several reports in the literature demonstrate the use of thin-layer chromatography (tlc) for identification of preservatives. The esters of *p*-hydroxybenzoic acid have been separated by tlc on silica gel G plates (2). Bark and Graham reported the tlc of 60 halogenated phenols on alumina plates using eight eluent systems (3). Baker and Booth separated halogenated salicylanilides on cellulose plates (4). More recently, tlc separation of several bacteriocides on silica gel GF_{254} was reported by Koenig (5) and by Braber *et al.* (6). Gunner determined methylenedioxy compounds by tlc–direct densitometry on Adsorbosil®* plates (7). These reports provide the basis for the current investigation.

Experimental

Apparatus and Materials

Apparatus used included a short wavelength UV light (Mineralight UVS 11†), tlc developing tank lined with filter paper, and spray apparatus (Chromaflex sprayer‡).

All preservatives were commercial grade and are listed in Table I. The solvent systems used were benzene-acetone (8:2) and chloroform-methanol (9:1).

Tlc plates (20 x 20 cm), both precoated by Analtech§ and prepared in this laboratory using silica gel GF_{254},** were used. Thickness in both cases was 250 μ. The F_{254} refers to fluorescence indicator added to silica gel.

Indicator Reagents

These included 4-aminoantipyrine-potassium ferricyanide (A), diazotized benzidine (B), and 4-methyl umbelliferone (C), each prepared as described by Stahl (8).

Chromotropic acid reagent (D) was prepared by carefully adding 15 ml of concentrated sulfuric acid to a solution of 1 g of sodium chromotropate in 15 ml of water. After spraying, the tlc plate was heated at 110–120°C for 10–30 min to achieve color development.

Acetylacetone reagent (E) was prepared as an aqueous solution by combining 0.2 ml of acetylacetone, 0.3 ml of glacial acetic acid, and 15.4 g of ammonium acetate in 100 ml of distilled water. After spraying, the tlc plate was heated at 110°C for 10 min to achieve color development.

Iodine vapor (F) was prepared by adding several crystals of iodine to a large beaker (about 2 l.) and warming on a steam bath. The tlc plate was held over vapors so that vapors contact silica gel surface.

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*Applied Science Laboratories Inc., State College, Pa.
†Ultraviolet Products, Inc., San Gabriel, Calif. 91778.
‡Kontes Glass Co., Vineland, N.J.. No. K-422540
§Brinkmann Instruments, Inc., Westbury, N.J. 11590.
**E. Merck, Dormstadt, W. Germany.

Table I

Preservatives and Sources

Preservative	Source
Bronopol®—2-Bromo-2-nitropropane-1,3-diol	Goldschmidt Chemical Co.
Butylated hydroxytoluene (BHT)	Analabs
Carvacrol—Isopropyl-*o*-cresol	Analabs
Chlorhexidine acetate—1,6-Di (*N*-*p*-chlorophenyl diguanido) hexane diacetate	Dr. Sylvan H. Newberger
4-Chloro-3-methyl phenol	Eastman Kodak
p-Chloro-*m*-xylenol (PCMX)	Eastman Kodak
Dehydroacetic acid (DAA)—3-acetyl-6-methyl-2H-pyran-2,4(3H)-dione	Eastman Kodak
Dichloro-*m*-xylenol (DCMX)	Eastman Kodak
Dichlorophene (DCP)	Sindar Corp.
Dimethoxane—6-Acetoxy-2,4-dimethyl-*m*-dioxane	Givaudan
Fluorsalan—3,5-Dibromo-3'-trifluoromethylsalicylanilide	Pfister Chemicals, Inc.
Germall 115®—Imidazolidinylurea	Sutton Labs
Hexachlorophene (HCP)	Nitene, Inc.
Irgasan CF_3®—Cloflucarban	Procter & Gamble
Irgasan DP 300®—Trichlosan	Ciba-Geigy
MDM hydantoin—Methyloldimethylhydantoin	Analabs
Octyl gallate	Eastman Kodak
o-Phenylphenol	Eastman Kodak
Propylparaben—Propyl-*p*-hydroxybenzoate	Eastman Kodak
Resorcinol	Eastman Kodak
Salicylanilide	Eastman Kodak
Tetrabromo-*o*-cresol—Deodorant K®	Biocosmetics Ltd.
Tribromsalan (TBS)—3,4',5-Tribromosalicylanilide	Fine Organics
Trichlocarban (TCC)—3,4,4'-Trichlorocarbanilide	Pfaltz & Bauer, Inc.
Vancide 89 RE®—*N*-Trichloromethylthio-4-cyclohexene-1,2-dicarboximide (Captan)	R. T. Vanderbilt Co., Inc.
Zinc pyrithione	Analabs

Methods

Preparation of Samples

Into a 50-ml beaker 0.2 g of sample was weighed. (A larger sample may be required to detect very low concentrations of preservatives.) Ethanol (25 ml) was added to the sample and mixed thoroughly. Any undissolved material was removed by filtration. The alcoholic solution was then evaporated to 5–10 ml on a steam bath under a jet of air. This solution was used for spotting the tlc plates as described below.

Thin-layer Chromatography of Sample

Preliminary Screening—Two separate tlc plates were spotted with 5–10 μl of the sample solution. One plate was developed with benzene-acetone

(8:2) and the other with chloroform-methanol (9:1). Each plate was allowed to develop until the solvent front migrated about 10 cm, then the plates were air-dried. The preservative was located as described below in Visualization of Preservatives.

Final Identification—The sample solution was spotted along with the standards of preservatives with similar R_f's on a new plate and developed as described above for preliminary screening.

Visualization of Preservatives

The following steps were taken to locate and identify the preservative:

The tlc plate was examined with a short wavelength UV light. A reddish-brown spot will indicate the presence of a UV-absorbing material which may

Table II

R_f Values and Results[a] with Indicator Reagents

Preservative	R_f		Detection by		
	C_6H_6-Acetone (8:2)	$CHCl_3$-MeOH (9:1)	UV	I_2	Indicator Reagents[b]
Bronopol	0.47	0.57			E, violet; F, yellow
Butylated hydroxytoluene	0.79	0.83		X	B, yellow
Carvacrol	0.65	0.75		X	A, pink; B, yellow
Chlorhexidine acetate	0.40	0.62	X		
4-Chloro-3-methyl phenol	0.59	0.65		X	
p-Chloro-*m*-xylenol	0.60	0.67		X	
Dehydroacetic acid	0.15	0.26	X		
Dichloro-*m*-xylenol	0.65	0.75		X	
Dichlorophene	0.50	0.62	X	X	
Fluorsalan	0.56	0.53	X		A, pink; B, yellow
Germall 115	0.00	0.00		X	C, pink; E, violet; F, yellow
Hexachlorophene	0.14	0.41	X	X	A, pink; B, yellow
Irgasan CF_3	0.53	0.67	X		
Irgasan DP 300	0.74	0.81		X	
MDM hydantoin	0.23	0.59			E, violet; F, yellow
Octyl gallate	0.12	0.22	X	X	
o-Phenylphenol	0.68	0.79	X	X	
Propylparaben	0.56	0.65	X	X	
Resorcinol	0.39	0.34	X	X	
Salicylanilide	0.65	0.72	X	X	A, pink; B, yellow
Tetrabromo-o-cresol	0.72	0.80	X		A, green; B, yellow
Tribromsalan	0.60	0.69	X		
Trichlocarban	0.55	0.70	X		
Vancide 89 RE	0.70	0.83			C, pink
Zinc pyrithione	0.49	0.82	X	X	

[a] Only positive tests are indicated.
[b] A, B, C, etc., refer to indicator reagents used.

be the preservative. The spots should be outlined with a spatula for future location.

A tank containing a few crystals of iodine was warmed and the tlc plate was placed into the I_2 vapors. Formation of brown spots will indicate the presence of organic compounds. The spots should be outlined for future location, as the iodine will gradually disappear.

The same tlc plate and/or additional plates was sprayed evenly with suggested spray reagents. Additional plates must be developed if more than one spray reagent is used, as the reagents form stable chemical derivatives.

R_f's for the located spots were calculated as follows:

$$R_f = \frac{\text{distance of spot center from start point}}{\text{distance of solvent front from start point}}$$

Results were then compared with standards to identify the preservative.

Results and Discussion

A total of 26 perservatives were examined by the described procedure, with the results shown in Table II. All preservatives except dimethoxane were detectable by one or more of the visualization procedures. The R_f values given

Table III

Results of Adding Preservatives to a Commercial Shampoo

Preservative	R_f Standard	R_f Shampoo	Detected by
Butylated hydroxytoluene	0.85	0.86	I_2
Carvacrol	0.67	0.66	I_2
p-Chloro-*m*-xylenol	0.59	0.58	I_2
Chlorhexidine acetate	0.59	0.60	I_2
4-Chloro-3-methyl phenol	0.60	0.61	I_2
Dehydroacetic acid	0.26	0.26	UV
Dichloro-*m*-xylenol	0.70	0.72	I_2
Dichlorophene	0.53	0.55	UV, I_2
Fluorsalan	0.54	0.57	UV
Germall 115	0.00	0.00	I_2; Reagent C
Hexachlorophene	0.35	0.33	UV, I_2
Irgasan CF_3	0.64	0.65	UV
Irgasan DP 300	0.68	0.68	UV
o-Phenylphenol	0.76	0.75	UV, I_2
Propylparaben	0.55	0.56	UV, I_2
Resorcinol	0.24	0.26	UV, I_2
Salicylanilide	0.73	0.74	UV, I_2
Tetrabromo-*o*-cresol	0.64	0.65	UV, very faint
Tribromsalan	0.60	0.60	UV
Trichlocarban	0.66	0.66	UV
Vancide 89 RE	0.81	0.81	Reagent C
Zinc pyrithione	0.78	0.76	UV, I_2

Table IV

Identification of Preservatives in Commercial Cosmetic Products

	Lotion		Lotion		Cream	
	R_f		R_f		R_f	
Preservative	Standard	Sample	Standard	Sample	Standard	Sample
Parabens	0.60	0.62	0.64	0.67	0.57	0.60
p-Chloro-*m*-xylenol	0.66	0.67	0.69	0.69	0.60	0.60
Tetrabromo-o-cresol	...	...	0.78	...	...	...
Irgasan DP 300	0.81	0.82	0.78	0.78	0.74	0.74
Dehydroacetic acid	0.15	0.17	...	...	0.27	0.24

Table V

Tlc of Cosmetic Products with Known Preservatives

Cosmetic Product	Preservative Claimed	Found
Deodorant soap	HCP[a], Tribromsalan	Tribromsalan
Deodorant soap	Tribromsalan, Trichlocarban, Irgasan CF-3	Tribromsalan, Trichlocarban, Irgasan CF-3
Deodorant soap	Tribromsalan	Tribromsalan
Deodorant soap	HCP[a], Trichlocarban	Trichlocarban
Deodorant soap	HCP[a]	
Deodorant soap	HCP[a]	
Shampoo	Dehydroacetic acid	Dehydroacetic acid
Hand lotion	Propylparaben	Propylparaben
Deodorant soap	Tribromsalan, Irgasan DP 300	Tribromsalan, Irgasan DP 300

[a] See text for discussion.

Table VI

Limit of Detectability of Several Preservatives

Preservative	UV (μg)	I_2 (μg)	Reagent A (μg)
Tribromsalan	0.1	0.1	0.5 violet
Hexachlorophene	0.5	0.1 faint	0.5 pink
Propylparaben	0.1	0.1	...
Trichlocarban	0.1	...	...
Dehydroacetic acid	0.5	...	...
p-Chloro-*m*-xylenol	0.5	0.1	0.5 purple
Tetrabromo-o-cresol	0.5	2 faint	0.5 blue

for the different solvent systems indicate that most of the preservatives could be identified by a combination of R_f value and characteristic reaction to the indicator. Vancide 89RE, Bronopol, and MDM hydantoin required a spray reagent for identification; all others could be located by UV and/or iodine vapor.

These preservatives were added to a shampoo to determine if the method was applicable to this type of cosmetic product. The results using the $CHCl_3$-MeOH solvent system are shown in Table III. Several preservatives were added to other cosmetic products and examined by the $CHCl_3$-MeOH system. Results are shown in Table IV.

Several cosmetics containing known preservatives were analyzed by the method described. The results shown in Table V indicate that the preservatives claimed were indeed found. In deodorant bars, R_f values for hexachlorophene (HCP) did not correspond to the standard HCP but were slightly higher. On one sample, the surfactant was removed by means of ion exchange* and gave better results.

The sensitivity of this tlc method was examined for several preservatives. Various amounts of each preservative were spotted and developed by the benzene-acetone solvent system. Results are shown in Table VI; the lowest detectable amount is indicated for UV light, iodine vapor, and 4-aminoantipyrine-potassium ferricyanide spray reagent.

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*Amberlite CK-400 Type 1, Strong Basic Anion Resin, Fisher Scientific Co., Pittsburgh, Pa. 15219.

Society of Cosmetic Chemists 1975 Officers Installed

At the December 3rd luncheon session of the Society's Annual Scientific Meeting at the Americana Hotel in New York City, 1974 President Dr. Hyman Henkin installed the Officers and Directors for 1975.

Left to right (seated): Treasurer Paul Thau, Director (Area II) Betty Lou Day, President Stephen G. Hoch, Secretary Gail Phillips Bucher, President-Elect Joseph H. Kratochvil; *(standing)* Director (Area I) Graham Barker, Director (Area III) Horst A. Ehrhardt, Director (Area 1) Mitchell L. Schlossman, Board Chairman Hyman Henkin, Director (Area I) George Pollack, and Director (Area II) Stanley E. Allured

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Aerobic Microflora of the Outer Eye Area of Women of Los Angeles, Calif.

JOHN F. McCONVILLE, B.S., and DAVID W. ANDERSON, Jr., Ph.D.*

Synopsis—Several reports have enumerated the MICROFLORA of used eye cosmetics. However, there is a paucity of literature describing the microflora of the OUTER EYE AREA. Understanding of the microflora of the outer skin around the eye should be useful in the development of PRESERVATIVE systems for eye cosmetics. The purpose of this paper is to contribute to the knowledge of the microflora of the outer eye as determined in selected subjects residing in Los Angeles, Calif.

Introduction

Knowledge of the microbiological flora present on the human face, in particular the eye area, is of importance to the cosmetic industry (1–5). The formulator of products for application on the human face should consider the types and numbers of microorganisms apt to be introduced into a product by applicators and/or fingers. Awareness of the resident and transient microorganisms found about the eye is useful in the development of ocular cosmetics in order to adequately preserve them against the survival of these microorganisms when introduced into the product by the consumer.

The purpose of this work was to define the numbers and types of aerobic microorganisms normally found on the outer eye and to ascertain if potentially pathogenic aerobic bacteria are found as residents or transients.

MATERIALS AND METHODS

Two separate studies were performed on two different groups of subjects selected from laboratory personnel. Various techniques have been employed in previous studies of the microflora present on human skin. However, because of the delicacy of the outer eye area, the method for sampling the microflora could not irritate the eye area of volunteer subjects. Also, we wanted the sampling method to simulate the application of eye area cosmetics. Thus, the

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standardized swabbing technique, although not totally consistent and reproducible, was the method of choice for sampling the microflora of the outer eye.

The first study involved a single swabbing of the eyebrow, the upper eyelid margin, and the lower eyelid margin of 21 subjects, both male and female. The second study involved four consecutive swabbings of the eyebrow and upper eyelid margin of five randomly selected female subjects to determine week-to-week variations of the outer eye microflora. In all cases, the swabbings were done during the day and all female subjects wore their usual make-up.

The swabbing technique employed presterilized, individually wrapped polyester fiber-tipped applicators* moistened with a sterile solution of 0.5% Polysorbate 80† in normal saline. The premoistened swabs were streaked four times over the area being sampled with concomitant twirling to insure full surface contact. Immediately after sampling, each swab tip was broken off into a 20 x 125-mm screw cap test tube containing 10 ml of Letheen broth (Difco).

All sample tubes were mixed by vortex for 1 min and 1 ml of each sample broth was serially diluted in sterile Polysorbate 80-saline. One milliliter of each sample dilution was plated in duplicate into Trypticase Soy Agar (TSA) for bacteria and Sabouraud's Dextrose Agar (SDA) for yeast and fungi. TSA plates were incubated at 35°C for 48 hours and SDA plates were incubated at 28°C for 5 days. The colonies found on these plates were reported as count per swab for the particular area examined.

Swab-broth tubes were incubated at 35°C for 24 hours and then one loopful of each was streaked onto a TSA plate for isolation of the bacteria present. The plates were incubated first at 35°C for 24 hours and then at room temperature for an additional 48 hours. Representative dissimilar colonies were gram-stained. Colonies of gram-positive spore-forming rods were considered as *Bacillus sp.* Colonies of gram-positive nonsporeforming rods resembling corynebacteria were considered lipophilic diphtheroids if the TSA colony was small and translucent, and as nonlipophilic diphtheroids if the TSA colony was large and dirty white.

Colonies of gram-negative rods were transferred to Eosin Methylene Blue Agar (BBL), MacConkey's Agar (BBL), Brilliant Green Agar (BBL), and Pseudomonas Isolation Agar (Difco). Isolated colonies on these differential agars were transferred to Triple Sugar Iron Agar (BBL) and Simmons Citrate Agar (BBL). Fermentative gram-negative rods were identified by the Pathotec "Rapid I-D System"®‡ and nonfermentative gram-negative rods were identified by a scheme of characteristics according to Pickett (6).

*Falcon Plastics, Los Angeles, Calif. 90045.
†Atlas Chemical, Division ICI America, Wilmington, Del. 19899.
‡General Diagnostics Division, Warner-Lambert Company, Morris Plains, N.J. 07950.

Table I

Quantitative Recovery of Aerobic Microorganisms from the Normal Outer Eye

Subject No.	Sex	Aerobic Plate Count per Swab		
		Eyebrow	Upper Eyelid	Lower Eyelid
1 JD	M	170	215	225
3 CA	M	980	850	8,100
4 BL	M	860	4,700	5,900
2 DA	F	14,400	6,900	55,000
5 MS	F	440	50	30
6 RAB	M	2,500	440	1,060
7 RB	F	20	330	150
8 MK	F	185	1,330	1,380
9 JG	F	50	230	60
10 MR	F	10,700	90,000	60,000
11 JM	M	1,600	80,000	70,000
12 JK	F	3,000	25,000	24,000
13 PM	F	230	10,000	7,000
14 JL	M	240	600	1,000
15 DH	F	1,800	650	8,000
16 CN	F	3,900	1,300	25,000
17 LB	F	600	1,300	2,500
18 BB	F	140	4,700	1,600
19 PJ	F	5,500	2,000	15,000
20 JP	F	750	6,000	10,000
21 RN	M	3,000	20,000	70,000

Results

Table I shows the quantitative results of the first study. The eyebrow area showed a range of 20 to 14,000 aerobic microorganisms per swab. The range for the eyelid margin was 50 to 90,000 organisms and for the lower eyelid margin 30 to 70,000. The number of microbes recovered varied greatly between subjects, but there was some consistency between the number of organisms recovered from the specific eye areas of each individual. Subjects with a low count on one area were consistently low on the other two areas. This trend was also apparent with those subjects in the high and medium count ranges. There was no correlation between the sex of the subjects and the number of microorganisms recovered which seems to be in agreement with Evans *et al.* (7).

Table II shows the aerobic microorganisms recovered from the eyebrow. The flora consisted mainly of *Staphylococcus epidermidis* and diphtheroids which are considered by most investigators as resident facial flora. *Staphylococcus aureus* and *Bacillus sp.* were found on three subjects while *Sarcina* and *Micrococcus flavus* were only recovered once.

Table II

Aerobic Microflora of the Eyebrow

Subject	APC[a]	Organisms Isolated
1 JD	170	*S. epidermidis*; diphtheroids
2 DA	980	*S. epidermidis*; diphtheroids
3 CA	860	*S. epidermidis*; diphtheroids
4 BL	14,000	*S. epidermidis*; diphtheroids; *M. flavus*[b]
5 MS	435	*S. epidermidis*
6 RAB	2,500	*S. epidermidis*; *Bacillus sp.*
7 RB	20	*S. epidermidis*
8 MK	185	*S. epidermidis*; diphtheroids
9 JC	50	*S. epidermidis*
10 MR	10,700	*S. epidermidis*; diphtheroids
11 JM	1,600	*S. epidermidis*; diphtheroids; *S. aureus*
12 JK	3,000	*S. epidermidis*; diphtheroids
13 PM	230	*S. epidermidis*; diphtheroids; *Bacillus sp.*
14 JL	600	*S. epidermidis*
15 DH	1,800	*S. epidermidis*; diphtheroids
16 CN	3,900	*S. epidermidis*; diphtheroids
17 LB	600	*S. epidermidis*
18 BB	140	*S. epidermidis*
19 PJ	5,500	*S. epidermidis*; diphtheroids; *S. aureus*; *Bacillus sp.*
20 JP	750	*S. epidermidis*; *S. aureus*
21 RN	3,000	*S. epidermidis*; diphtheroids; *Sarcina*

[a]Aerobic plate count per swab.
[b]*Micrococcus flavus*.

The microflora of the upper eyelid (Table III) and the lower eyelid (Table IV) were comparable and more complex than that of the eyebrow. *S. epidermidis* was found on the upper and lower eyelid of all subjects. Diphtheroids were found on the upper eyelid of 18 of the 21 subjects and on the lower eyelid of 19 subjects. *M. flavus*, *S. aureus*, and *Bacillus sp.* were found more frequently on the eyelid margins than on the eyebrow. *A. anitratus* was recovered from four individuals one of which also harbored *Klebsiella* on her upper and lower eyelid margin. Two species of fungi were recovered in low numbers from two individuals.

Table V represents the week-to-week fluctuations in the microflora of the outer eye of five female subjects, all of whom wore eye make-up regularly. These subjects showed weekly variations in the number of aerobic microorganisms recovered by swabbing. Subjects 24, 25, and 26 had variations in the types of organisms present from one week to another. These data indicate the outer eye microflora to be dynamic, with any sampling being representative of the subject only at the time of sampling.

Only *S. epidermidis* was recovered from subject 23 on all four weekly samplings. Further investigation of her make-up habits revealed that she ap-

Table III

Aerobic Microflora of the Upper Eyelid Margin

Subject	APC[a]	Organisms Isolated
1 JD	215	*S. epidermidis;* diphtheroids
2 DA	850	*S. epidermidis;* diphtheroids
3 CA	4,700	*S. epidermidis;* diphtheroids; *M. flavus*[b]
4 BL	13,000	*S. epidermidis;* diphtheroids; *S. aureus*
5 MS	50	*S. epidermidis*
6 RAB	440	*S. epidermidis;* diphtheroids; *Bacillus sp.*
7 RB	330	*S. epidermidis;* diphtheroids
8 MK	1,330	*S. epidermidis; S. aureus*
9 JG	230	*S. epidermidis*
10 MR	90,000	*S. epidermidis;* diphtheroids; *M. flavus*
11 JM	80,000	*S. epidermidis;* diphtheroids; *S. aureus*
12 JK	25,000	*S. epidermidis;* diphtheroids; *M. flavus*
13 PM	16,000	*S. epidermidis;* diphtheroids; *A. anitratus*[c]
14 JL	600	*S. epidermidis;* diphtheroids; *Aspergillus sp.*
15 DH	650	*S. epidermidis;* diphtheroids; *M. flavus*
16 CN	1,300	*S. epidermidis;* diphtheroids; *M. flavus*
17 LB	1,300	*S. epidermidis;* diphtheroids; *Klebsiella; A. anitratus*
18 BB	4,700	*S. epidermidis;* diphtheroids; *Bacillus sp.*
19 PJ	2,000	*S. epidermidis;* diphtheroids; *S. aureus*
20 JP	6,000	*S. epidermidis;* diphtheroids; *S. aureus; M. flavus*
21 RN	20,000	*S. epidermidis;* diphtheroids; *Sarcina; Aspergillus sp.; Bacillus sp.*

[a]Aerobic plate count per swab.
[b]*Micrococcus flavus.*
[c]*Acinetobacter antitratus.*

plied a facial cleanser containing 2% sulphur and 1.5% salicylic acid daily before applying her make-up.

P. aeruginosa was recovered from the eyebrow and upper eyelid of subject 22 on each sampling. Since this microorganism is not a usual resident of the human facial flora, we continued swabbing this subject twice weekly for two months expanding our testing to the cheek, forehead, and hands. *P. aeruginosa* was found on all of the areas sampled. Examination of her cosmetics showed them to be free from *P. aeruginosa.*

Discussion

In the first study of 21 male and female subjects, three eye areas were swabbed to determine the number and types of aerobic microorganisms one might expect to find on the orbital area. Although aware that anaerobic microorganisms outnumber the aerobic flora on the human skin (8, 9), we confined this study to aerobes since they have been most frequently isolated from some cosmetics. Because the Los Angeles climate is temperate and dry, we had not

Table IV

Aerobic Microflora of the Lower Eyelid Margin

Subject	APC[a]	Organisms Isolated
1 JD	225	*S. epidermidis*
2 DA	8,100	*S. epidermidis;* diphtheroids
3 CA	5,900	*S. epidermidis;* diphtheroids; *M. flavus*[b]
4 BL	55,000	*S. epidermidis;* diphtheroids; *S. aureus*
5 MS	30	*S. epidermidis*
6 RAB	1,060	*S. epidermidis;* diphtheroids; *Bacillus sp.*
7 RB	150	*S. epidermidis;* diphtheroids
8 MK	1,375	*S. epidermidis;* diphtheroids; *S. aureus*
9 JG	60	*S. epidermidis*
10 MR	60,000	*S. epidermidis;* diphtheroids; *M. flavus*
11 JM	70,000	*S. epidermidis;* diphtheroids; *S. aureus*
12 JK	24,000	*S. epidermidis;* diphtheroids; *M. flavus; A. anitratus*[c]
13 PM	7,000	*S. epidermidis;* diphtheroids
14 JL	1,000	*S. epidermidis; Aspergillus sp.*
15 DH	8,000	*S. epidermidis;* diphtheroids; *M. flavus; Bacillus sp.*
16 CN	25,000	*S. epidermidis;* diphtheroids; *M. flavus; Bacillus sp.*
17 LB	2,500	*S. epidermidis;* diphtheroids; *Klebsiella; A. anitratus*
18 BB	1,600	*S. epidermidis;* diphtheroids; *Bacillus sp.; A. anitratus*
19 PJ	15,000	*S. epidermidis;* diphtheroids; *S. aureus*
20 JP	10,000	*S. epidermidis;* diphtheroids; *S. aureus; M. flavus*
21 RN	70,000	*S. epidermidis;* diphtheroids; *Bacillus sp.; Sarcina; Aspergillus sp.; Paecilomyces*

[a]Aerobic plate count per swab.
[b]*Micrococcus flavus.*
[c]*Acinetobacter anitratus.*

expected to encounter a large variety of yeasts and molds. Results substantiate this expectation since fungi were recovered in low numbers from only two subjects. In contrast, Wilson *et al.* (10) recovered numerous species of yeast and fungi from the eyes of 29 of 138 women in Atlanta, Georgia. Geographical location is probably an important factor when evaluating normal facial flora.

The number of microorganisms recovered varied greatly between subjects but the number of microbes recovered from the three eye areas of each individual was fairly consistent. Hygiene and the inherent properties of a person's skin most probably would have an effect on their microbial population and should be taken into consideration when evaluating normal flora. A person with dry skin or one who laboriously scrubs the facial area would not be expected to maintain as great a microbial population as someone with oily skin practicing less rigorous cleansing habits.

Normal flora may be defined as those organisms which are consistently recovered from the individuals tested (8). In this study, *S. epidermidis* and diphtheroids may be considered normal flora. But *S. aureus* and

Table V

The Microflora of the Outer Eye Area as Determined by Swabbing Once a Week for Four Consecutive Weeks

		Aerobic Plate Count per Swab		
Subject	Week	Upper Eyelid	Eyebrow	Microflora Found
22 CM	1	12,700	1,360	*S. epidermidis; P. aeruginosa*
	2	3,100	2,400	*S. epidermidis; P. aeruginosa*
	3	5,000	4,400	*S. epidermidis; P. aeruginosa*
	4	1,800	180	*S. epidermidis; P. aeruginosa*
23 TR	1	2,000	1,900	*S. epidermidis*
	2	1,600	1,500	*S. epidermidis*
	3	2,200	4,500	*S. epidermidis*
	4	4,100	4,000	*S. epidermidis*
24 BD	1	6,200	14,400	*S. epidermidis;* diphtheroids; *Bacillus sp.*
	2	1,700	12,700	*S. epidermidis;* diphtheroids
	3	860	400	*S. epidermidis;* diphtheroids; *Bacillus sp.*
	4	1,700	600	*S. epidermidis*
25 DA	1	6,800	2,980	*S. epidermidis;* diphtheroids; *Bacillus sp.*
	2	3,700	5,800	*S. epidermidis;* diphtheroids; *Bacillus sp.*
	3	2,500	1,900	*S. epidermidis;* diphtheroids
	4	1,800	450	*S. epidermidis*
26 EB	1	8,500	4,100	*S. epidermidis;* diphtheroids; *Bacillus sp.*
	2	17,000	4,700	*S. epidermidis;* diphtheroids; *Bacillus sp.*
	3	2,140	2,110	*S. epidermidis*
	4	1,100	1,200	*S. epidermidis;* diphtheroids; *A. anitratus*

M. flavus were also recovered from more than half of the subjects tested. Perhaps these organisms could be considered normal flora of the outer eye for Los Angeles subjects.

Further testing of this particular group of subjects would have to be done over a prolonged period of time before this question could be answered. One might find that these microorganisms would only be recovered consistently from a few individuals and therefore would be considered as normal flora for the individual, but not for the group as a whole.

In our second study, we tested five individuals weekly for 4 weeks to determine if there would be fluctuations in numbers and types of micro-

organisms recovered. The results show that the types of organisms recovered were fairly consistent, but the numbers varied as much as 30-fold. S. *epidermidis* and diphtheroids were the two organisms recovered consistently from most of the subjects. It should be mentioned, however, that in this and another study (11), the wearing of nonmedicated or regular face and eye make up did not affect the flora of the subjects studies. As noted earlier, only S. *epidermidis* was recovered from subject 23. The use of the medicated cleanser may account for the absence of other flora.

On each sampling, *P. aeruginosa* was found on the outer eye of subject 22, and subsequent swabbing of her cheek and forehead showed this organism to be predominant. Further investigation revealed a history of chronic ear problems manifested by itching and occasional discharge. Swabbing of her ears and subsequent streaking directly on TSA plates showed heavy confluent growth on the agar surfaces after 24 hours. Isolation and differentiation of the microorganisms revealed a flourescent and a nonflourescent strain of *P. aeruginosa*.

Since this subject had a chronic ear infection for several years, undoubtedly *P. aeruginosa* was a part of her facial flora for some time. Yet this organism would not be considered normal flora since it disappeared from her facial area upon relief of the infection of the external auditory canals. Further study of this subject is presented elsewhere (12).

A knowledge of the normal flora is important to the cosmetic microbiologist when developing preservative systems. Cosmetic products may receive a daily inoculation over a considerable period of time. Considering geographical distribution of these products and other factors, the inoculations may consist of yeasts, molds, and both gram-negative and gram-positive bacteria. Transient organisms should not be overlooked as possible product inocula.

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Society of Cosmetic Chemists Medal Award to Dr. Martin M. Rieger

The Society of Cosmetic Chemists presented its 1974 Medal Award to Dr. Martin M. Rieger, Associate Director of Long-Term Development in the Personal Products Division of Warner-Lambert Company, Morris Plains, N.J. The Medal Award, the Society's highest honor, was presented to Dr. Rieger in recognition of the many contributions he has made over the years to the cosmetic and toiletries industry and to the Society of Cosmetic Chemists organization in particular.

The formal presentation was made at the December 2nd luncheon during the Society's Annual Scientific Meeting by Dr. Hyman Henkin, 1974 SCC President, and Mr. Charles Fox, a long-time colleague of Dr. Rieger, acted as Eulogist.

Left to right: Medal Award Chairman Lester I. Conrad, Society President Hyman Henkin, Medalist Martin M. Rieger, and Eulogist Charles Fox

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Resorptionsmöglichkeiten der Haut

F. MEYER* und J. ZIEGENMEYER*

Nach einem Vortrag anläßlich der Tagung der Gesellschaft Deutscher Kosmetik-Chemiker e. V. in Baden-Baden, 13.—15. 3. 1974

Synopsis—The Absorption Potential of Skin. — PENETRANTS are defined as materials which can transport actives into the CORIUM OF SKIN and act as ACCELERATORS OF ABSORPTION. Transport into the corium appears to occur in toto without any appreciable selectivity. Within the epidermis the penetrant evidently loses its efficacy, and transport becomes increasingly dependent on the active. The velocity of PERCUTANEOUS ABSORPTION can be exceedingly high. Thus the presence of DYES in the corium or the ACTION OF LIDOCAINE can be demonstrated already 15 minutes after EXTERNAL APPLICATION. Differences in absorption between LABORATORY ANIMALS and MAN can be expected and are related, in part, to the thickness of the epidermis and the density of hair. Finally, it has been known for some time that DISEASED, DAMAGED, or AGED SKIN has an altered ability to absorb foreign materials. The behavior in the skin will, of course, have a major influence on CAPILLARY ABSORPTION. Depot action in the epithelium must also be considered since resorption can continue even after termination of external contact. This appears particularly important in the case of COSMETICS since, in principle, ACCELERATION OF PENETRATION is possible. Sometimes, this is desirable for an INTENTIONAL "DEEP" ACTION. Often, it will however be less desirable because the unavoidable absorption cannot be controlled. It is not certain whether and to what degree penetrants or the subsequent interference with penetration can be used to generate meaningful effects in deeper layers of the skin. In principle it appears at least theoretically possible to control the depth of penetration. On the other hand, it is frequently methodologically extremely difficult to describe the required parameters quantitatively. Overall, the TECHNOLOGICAL EFFORTS OF COSMETIC RESEARCH should be supported more than previously by ANIMAL EXPERIMENTATION. This will permit an early determination whether percutaneous absorption of materials from cosmetic preparations can occur or can be precluded.

Auch eine intakte Haut schützt den Organismus nicht vollständig gegen äußere chemische Einflüsse. Aus der Toxikologie ist z. B. die percutane Aufnahme von Alkylphosphaten, Phenolen, Salicylsäurederivaten und Hexachlorophen seit langem bekannt. Äußerlich applizierte Substanzen können somit die Haut durchdringen und auf diesem Wege in den allgemeinen Kreislauf gelangen. Sie ist eben doch durchlässig für eine in ihrer Gesamtheit noch

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nicht übersehbare Anzahl von Verbindungen. Die Frage, welcher Stoff in welchem Umfang die Hautschranken passiert und welchen Veränderungen er bis zu seiner Ausscheidung unterliegt, ist für die Toxikologie oder die externe Therapie mit Arzneistoffen ebenso von großer praktischer und theoretischer Bedeutung, wie für den sinnvollen Einsatz kosmetischer Präparate. Hierbei spielen physiko-chemische Eigenschaften der Vehikelsubstanzen wie der Wirkstoffe, ihre Konzentrationen in der Zubereitung, die Dauer der Applikation, die Größe der Kontaktfläche und der Zustand der Haut eine wesentliche Rolle. Viele, auch neuere, Ergebnisse sind mehrdeutig (1).

Imbibition, Penetration und Resorption (Absorption) sollten klarer unterschieden werden: Imbibition beinhaltet nur die Durchtränkung oberflächlicher Epithelschichten mit einer äußerlich applizierten Zubereitung. Sie kann mehr oder weniger tief eingedrungen sein, ohne jedoch die physiologische Schutzfunktion der Epidermis durchbrochen zu haben. Im Falle einer Penetration hat der Stoff in der Zubereitung oder haben Inhaltsstoffe derselben das Epithel vollständig passiert, somit auch die sogenannte Szakallsche Barriere überwunden und das Stratum germinativum erreicht. Erst dann können Substanzen ins Corium gelangen. Sie lassen sich hier häufig nachweisen und dokumentieren auf diese Weise eine erfolgreiche Penetration. Letztere ist somit unabdingbare Voraussetzung für percutane Resorption oder Absorption, die Aufnahme in den Organismus. Sie wird mit dem Abtransport in den allgemeinen Kreislauf beendet. Da sich aber Lymph- und Blutgefäße erst im Corium befinden, ist eine Resorption frühestens von hier aus möglich. Neben dieser transepidermalen ist wohl nur noch die transfollikuläre Aufnahme von nennenswerter praktischer Bedeutung. Aber auch in diesem Fall ist das Corium die entscheidende Station für die Resorption.

Unsere pharmakologischen Untersuchungen hatten zunächst das Ziel, viel Wirkstoff möglichst schnell und gegebenenfalls exakt dosiert percutan zur Resorption zu bringen. Kosmetische Aspekte hinsichtlich Eindringtiefe, Depotwirkung, Steuerung derselben oder des Abtransportes ergeben sich daher erst in zweiter Linie. Für einen Kosmetika-Chemiker sind diese Befunde aber insofern interessant, als sie zeigen, daß sich nach einer, wenn auch unbeabsichtigten, Penetration eine Resorption kaum noch verhindern läßt. Sie kann auch dann noch eintreten, wenn der äußere Kontakt bereits lange unterbrochen ist. Kosmetische Wirkstoffe wird man somit in der Epidermis, im Stadium der Imbibition, zu halten trachten.

Gewisse organische Lösungsmittel schleusen andere Stoffe, die nicht oder nur sehr langsam penetrieren, durch die Hautbarriere und bringen sie so percutan zur Resorption. Diese Penetrationsvermittler erfüllen ihre Funktion weitgehend unabhängig vom eigentlichen Wirkstoff. Träger, Substanz und gegebe-

nenfalls vorhandene Lösungsvermittler scheinen zusammen aufgenommen zu werden, in toto also, offenbar ohne nennenswerte Selektion im Epithel. Hierbei handelt es sich vorwiegend um einen interzellulären transepidermalen und transfollikulären, passiven Transport.

Seit Jahrzehnten zählt Eserin, ein Cholinesterasehemmstoff, zu den Indikatoren einer möglichen Penetrationsvermittlung (2) (3). Seine Wirkung auf die quergestreifte Muskulatur ist ausgeprägt und kann nach Resorption sehr kleiner Mengen im tierischen Organismus verhältnismäßig leicht nachgewiesen werden. Registriert wird z. B. der Effekt auf die periodisch elektrisch gereizte Kaumuskulatur von Mäusen, wobei der Zeitraum vom Beginn der äußeren Applikation auf die intakte Haut bis zum Anstieg der Hubhöhe die Resorption und ihre Geschwindigkeit anzeigt.

Die Untersuchung primärer, einwertiger Alkohole ließ folgendes erkennen: Erst ab Verbindungen mit 4 C-Atomen setzte allmählich ein schwacher Eserin-Effekt ein. Er steigerte sich mit wachsender Kohlenstoffanzahl und hatte sein Optimum bei Alkoholen von mittlerer Kettenlänge. Iso-Alkohole permeierten die Haut mit gleicher Geschwindigkeit wie unverzweigte, sekundäre dagegen merklich langsamer als primäre. Mehrwertige Alkohole wirkten selbst nach zweistündigem Kontakt nicht meßbar (4).

Ein weiterer Nachweis percutaner Resorption kann mit dem herzwirksamen Glykosid Convallatoxin geführt werden, welches die intakte Haut normalerweise in erkennbarer Menge nicht durchdringt (5). Mit Hilfe geeigneter Penetrationsvermittler indessen läßt es sich percutan zur Resorption bringen, sogar in tödlichen Dosen, und selbst von einer kleinen Oberfläche aus. Um Convallatoxin in der gewünschten Konzentration von 1,5 mg/Tier vergleichend untersuchen zu können, mußten Lösungsvermittler verwendet werden, die in bezug auf die Penetration und die Resorptionsgeschwindigkeit des Wirkstoff-Trägergemisches indifferent blieben, wie Kontrolluntersuchungen bestätigt haben. Aus der bei venöser Verabfolgung tödlichen Dosis, der extern angebotenen Wirkstoffmenge und der Kontaktfläche ergibt sich ein Anhalt für die Resorptionsgeschwindigkeit. Sie beträgt einige $mm^3/cm^2/h$.

Wie aus *Tabelle 1* ersichtlich, penetrieren Hexan und Hexen beträchtlich schneller durch die intakte Meerschweinchenhaut als die entsprechenden Alkohole, denn in den Kohlenwasserstoffen gelöstes Convallatoxin führt erheblich schneller zum Tode, wird demnach rascher resorbiert als aus Hexanol und Hexen-3-ol (6). Unter gleichen Bedingungen bleiben mehrwertige Alkohole wirkungslos wie auch schon bei den geschilderten Versuchen mit Eserin.

Mit Hilfe eines speziellen Aggregates lassen sich die genannten und auch andere Wirkstoffe exakt dosiert percutan zur Aufnahme bringen, mit einer Resorptionsquote von nahezu 100 % (7). Das Prinzip besteht darin, daß der

Tabelle 1

Percutane Applikation von 1,5 mg Convallatoxin pro Meerschweinchen unter Verwendung verschiedener Träger- und Schleppersubstanzen.

Träger	Anteil in Vol.-%	Versuchsanzahl	Exitus letalis in min	Resorptionsgeschwindigkeit $mm^3/cm^2/h$	
Hexan	50	6	68	7,7	
Hexanol	25				
Cyclohexanon	25				
Hexanol n-prim.	75	11	137	3,2	
Cyclohexanon	25				
1-Hexen	55	44	76	5,3	
Cyclohexanon	45				
1-Hexen-3-ol	75	4	300	1,6	
Cyclohexanon	25				
Äthylglykol	100	2	nach 24 Stdn.	< 0,5	
1,2-Propylenglykol	100	2	nach 24 Stdn.	< 0,5	
Glycerin	70	2	nach 24 Stdn.	< 0,5	ohne
Methanol	29				Befund
Äthylglykol	1				
Methanol	100	2	nach 24 Stdn.	< 0,5	
Äthanol	70	2	nach 24 Stdn.	< 0,5	
Methanol	30				

aus einer Speicherschicht stammende Penetrationsvermittler über Dochte in eine Wirkstoffträgerschicht geleitet wird, dort die Sustanz eluiert und sie anschließend durch die Haut transportiert.

Neben diesen Indikatoren erfolgter Aufnahme, die sich post resorptionem aufgrund ihrer Wirkung erkennen lassen, sind Farbstoffe geeignet, die Hautresorption selbst sichtbar zu machen. Ihre Diffusion in tiefere Schichten der Haut kann nach Anfertigung von Gefrierschnitten im Mikroskop verfolgt werden. Neben Malachitgrün, das uns als Chemotherapeutikum interessierte, haben wir vorwiegend Rhodamin B untersucht, das stark fluoresciert und daher auch bei sehr geringer Schichtdicke im Fluorescenzmikroskop sichtbar wird. Unterschiedliche Intensität der Fluorescenz im Corium kann mit der aufgenommenen Menge Farbstoff korreliert werden und zeigt die Wirksamkeit von Penetrationsvermittlern unmittelbar an. Sie läßt sich nach folgendem

Schema ganz gut beurteilen: 0 = keine, 1 = geringe, 2 = deutliche, 3 = starke, 4 = sehr starke Fluorescenz im Corium. Rhodamin B penetriert wie Eserin oder Convallatoxin nicht, auch nicht in wäßriger oder Äthylenglykolmonoäthyläther-Lösung. Selbst nach stundenlanger äußerer Einwirkung beschränkt sich die Fluorescenz auf die äußere Behaarung und die obersten Schichten des Epithels, es kommt somit lediglich zur Imbibition. Wird einer Rhodamin B-Lösung in Äthylenglykolmonoäthyläther ein penetrierender Kohlenwasserstoff, z. B. Cyclohexan, hinzugegeben, so erscheint das fluorescierende Rhodamin nicht nur in den Haarschäften, sondern auch, wengleich etwas vermindert, in ihrer Umgebung. Eine äußerliche Applikation von nur 10 min Dauer reicht bereits aus, eine deutliche Fluorescenz im Corium hervorzurufen. Sie vertieft sich erheblich nach Verlängerung der Kontaktzeit, nach 2 Stdn. z. B. fluoresciert das gesamte Corium sehr stark, sogar das subcutane Fettgewebe und die darunter liegende Muskulatur.

Ähnliche Versuche haben wir mit Tetracyclinen durchgeführt (8). Sie fluorescieren intensiv genug, um im Gewebe auf die gleiche Weise sichtbar gemacht zu werden. Der Befund im Corium ist negativ nach Applikation von Handelssalben mit therapeutisch üblichen Tetracyclindosierungen, auch nach Verlängerung der Einwirkzeit auf 20 Stdn. oder Erhöhung der Wirkstoffkonzentration auf 10% *(Tabelle 2)*. Im Gegensatz hierzu können Penetrationsvermittler aus

Tabelle 2

Dermale Applikation verschiedener tetracyclinhaltiger Salben auf die intakte Haut von Meerschweinchen.

Wirkstoff(e)	Konzentration Gew.-%	Einwirkdauer in Stdn.	Fluorescenz im Corium
Tetracyclin [1]	1		
Tetracyclin	3		
Tetracyclin [1]	3		
Chlortetracyclin	3		
Oxytetracyclin [2]	0,45	2, 20	keine
Oxytetracyclin	1,5		
Oxytetracyclin [2]	3,24		
Oxytetracyclin	9,72		
Oxytetracyclin	10,0		

Handelsbezeichnungen: Achro-, Aureo-, Terramycin

[1]) neben Hydrocortison

[2]) neben Polymyxin

der Reihe der Kohlenwasserstoffe, z. B. Tetradecen, Dodecen, Cyclohexan, beträchtliche Wirkstoffmengen in tiefe Schichten der Haut transportieren. Diese Befunde lassen sich an allen üblichen Laboratoriumstieren prinzipiell in gleicher Art reproduzieren, interessanterweise auch an der Rhinozeros-Maus, die keine intakten Haarfollikel besitzt. Die Fluorescenzwerte im Corium stimmen mit denen bei anderen Tieren gefundenen überein, obwohl der Wirkstoff im wesentlichen nur auf transepidermalem Wege dorthin gelangt sein dürfte *(Tabelle 3)*.

Tabelle 3

Percutane Aufnahme von 2,5 Gew.-% Oxytetracyclin-hydrochlorid durch die Haut verschiedener Tierspezies.

	AGMA	Dimethylsulfoxid *)	Cyclohexan *)	Dodecen *)	Tetradecen *)
Meerschweinchen	0	2,5	4	4	3,75
Maus	0	2,5	4	3,5	
Rhinozeros-Maus	0	2	4	4	
Ratte	0	2,5	3,5	4	
Kaninchen	0	2,5	4	4	
Katze	0	2	4	4	
Hund	0	2,3	3,3	3,3	

*) neben 50 Vol.-% Äthylenglykolmonoäthyläther (AGMA) als Lösungsvermittler. Beurteilung der Fluorescenzintensität im Corium: 0 = keine, 1 = geringe, 2 = deutliche, 3 = starke, 4 = sehr starke.

Bei percutaner Verabfolgung liegt die fluorescenzmikroskopische Nachweisgrenze im Gefrierschnitt für Oxytetracyclin bei 0,1 %. Es ist die gleiche Größenordnung, die sich nach subcutaner Injektion abnehmender Dosen in wäßrigen Lösungen ergibt. Dieser Befund spricht dafür, daß die äußerlich aufgetragene Konzentration mit derjenigen übereinstimmt, die im Corium erscheint. Auf dem kurzen Weg dorthin erfolgt offenbar keine nennenswerte Selektion.

Außer den vorgenannten haben wir zahlreiche andere Substanzen auf eine mögliche Penetration geprüft: Aconitin, g-Strophantin, k-Strophantin, Phenobarbital, Promethazin, Diphenhydramin, Doxylamin, Fomocain, Lidocain, Procain, Vitamin A, Porphyrin, Salicylsäure-Derivate, 5-Chlor-8-hydroxychinolin, 5,7-Dichlor-8-hydroxychinolin, Orcein. Sie alle sind für den Nachweis einer percutanen Aufnahme geeignet. Vor allem stellte sich heraus, daß jeweils dieselben Penetrationsvermittler im gleichen Maß wirksam sind. Hier-

aus schließen wir, daß der Wirkstoff während der Penetrationsphase nur eine untergeordnete Bedeutung hat, zumindest in den Grenzen der Molekülgrößen der oben angegebenen Verbindungen.

Weiterhin haben wir die Frage zu beantworten versucht, welche physikochemischen Voraussetzungen ein organisches Vehikel erfüllen muß, um eine Penetration vermitteln zu können. Neben Kohlenwasserstoffen und Alkoholen haben wir Aldehyde, Ketone, Ester, ätherische Öle und ihre Inhaltsstoffe, nitrierte Verbindungen, Alkylhalogenide, Alkylphosphate, im ganzen einige hundert Flüssigkeiten untersucht. Hierbei hat sich folgendes ergeben: Wenn Penetrationsvermittlung in einzelnen Verbindungsklassen gefunden wurde, gab es meist auch ein Optimum bei Substanzen mit mittlerer Kettenlänge. *Abb. 1* zeigt diesen Zusammenhang: Die Intensität der Rhodaminfluorescenz im Corium ist in Abhängigkeit von der Anzahl der C-Atome in der Reihe der Alkane, Alkene und primären Alkohole aufgeführt. Alkane und Alkene haben

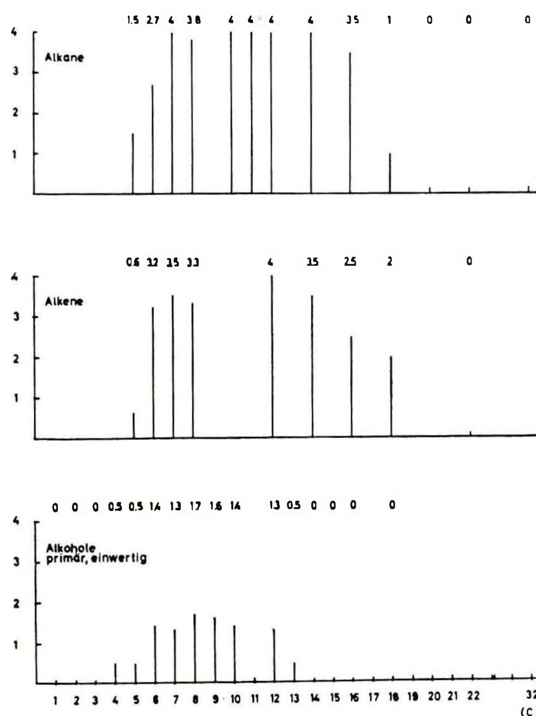

Abbildung 1

Penetrationsvermögen verschiedener Alkane, Alkene und primärer einwertiger Alkohole durch die intakte Haut von Meerschweinchen.
Ordinate: Intensität der Fluorescenz von Rhodamin B im Corium
Abszisse: Anzahl der C-Atome (C)

ihr Optimum bei 6 bis 16 C-Atomen, primäre Alkohole zwischen 6 und 12 C-Atomen. Im ganzen sind letztere jedoch weniger wirksam als ihre entsprechenden Kohlenwasserstoffe.

Die vergleichende Gegenüberstellung von Verbindungen mit jeweils 6 C-Atomen ließ erkennen, daß Kohlenwasserstoffe (n-Hexan, 1-Hexen, *cis*, *trans* 2-Hexen, 1-Hexin, Cyclohexan, Benzol) die besten Penetrationseigenschaften besitzen. Für ihr Verhalten scheinen gesättigte oder ungesättigte aliphatische, cycloaliphatische oder aromatische Strukturen keine wesentlichen Unterschiede zu begründen. Auch unter den geprüften Isomeren gibt es keine signifikanten Differenzen: 2,2-Dimethylbutan, 2,3-Dimethylbutan, 2-Methylpentan, 3-Methylpentan, 2-Methyl-1-pentan, 4-Methyl-1-pentan, *cis*-4-Methyl-1-penten, *trans*-4-Methyl-1-penten, Methylcyclopentan, Methylcyclopentadien. Einwertige Alkohole waren weniger effektiv: n-Hexanol, 2,2-Dimethyl-1-butanol, 2-Methyl-3-pentanol, 2,2-Dimethyl-3-butanol, 3-Methyl-3-pentanol, 3-Hexen-1-ol, Cyclohexanol, Benzylalkohol. Diole (2-Methylpentan-2,4-diol, 3-Methylpentan-2,4-diol, Cyclopentandiol) führen keine Fluorescenz im Corium herbei, nitrierte Kohlenwasserstoffe ebenfalls nicht (Nitrohexan, Nitrocyclohexan, Nitrobenzol), Ketone eine nur geringe (3-Methyl-2-pentanon, 4-Methyl-2-pentanon, 4-Methyl-3-pentanon, 2,2-Dimethyl-3-butanon, 2-Methyl-2-penten-4-on, Cyclohexanon).

Verbindungen mit 8 C-Atomen weisen die gleichen Eigenschaften auf: Kohlenwasserstoffe wie n-Octan, 1-Octen penetrierten am besten, ebenfalls ihre Isomeren: Ein Octan-Isomerengemisch, 3-Methyl-heptan, 2,5-Dimethyl-2,4-hexadien, *cis*-1,2-Dimethylcyclohexan, *trans*-1,2-Dimethylcyclohexan, 1,3-Dimethylcyclohexan, 1,4-Dimethylcyclohexan, Äthylbenzol, Dimethylbenzol (o-, m-, p-Xylol). C_8-Alkohole fluorescierten weniger intensiv: n-Octanol, 3-Methyl-2-heptanol, 6-Methyl-2-heptanol, 5-Methyl-3-heptanol, sek. Octanol, 2,5-Dimethylcyclohexanol, 3,4-Dimethylcyclohexanol, 3,5-Dimethylcyclohexanol. Noch schwächer waren Ketone: 6-Methyl-2-heptanon, 3-Methyl-2-heptanon, 4-Methyl-3-heptanon, 5-Methyl-3-heptanon, 2-Methyl-4-heptanon, 6-Methyl-5-hepten-2-on, 2,4-Dimethyl-2,5-heptadien-on. 3-Methylheptan-2,4-diol ist unwirksam.

Welche physikalisch-chemischen Eigenschaften die percutane Aufnahme einer Verbindung in den Organismus begründen, läßt sich bislang noch nicht eindeutig festlegen. Zwar werden in der Literatur einige oft genannt und für die Hauptpermeabilität verantwortlich gemacht, z. B. die Lipidlöslichkeit, der Verteilungskoeffizient oder ähnliches (9) (10), aber diese Kriterien ändern sich bekanntlich auch mit der Kettenlänge. Differenzen zu entsprechenden Theorien ergeben sich vor allem dann, wenn eine größer Zahl von Substanzen auf Übereinstimmungen zwischen Penetrationsvermögen und Stoffeigenschaften hin

geprüft wird, wie es Stemann getan hat (11): Der Penetrationsgrad der Verbindungen wurde am Ausmaß der Fluorescenz im Corium gemessen und mit ihrem Lösungsvermögen in Cholesterin und Stearinsäure korreliert. Stemann konnte zeigen, daß die Penetration mit steigender Löslichkeit in diesen Stoffen nicht zunahm. Es gibt Verbindungen, die ausgezeichnet penetrieren, ohne Stearinsäure oder Cholesterin besonders gut zu lösen, und wiederum solche, die für diese ein hervorragendes Lösungsvermögen besitzen, die Haut aber nicht permeieren. Der äußerliche Lipidfilm der Haut spielt demnach kaum die entscheidende Rolle für eine percutane Penetration.

Die Korrelation der Penetration mit der Wasserlöslichkeit ergibt offenbar eine weit bessere Beziehung. Verbindungen mit geringer Wasserlöslichkeit penetrieren gut, z. B. Kohlenwasserstoffe. Andere mit Wasser in jedem Verhältnis mischbare Substanzen durchdringen die Haut offenbar kaum. Hiervon gibt es nur wenige Ausnahmen, z. B. Dimethylsulfoxid (DMSO).

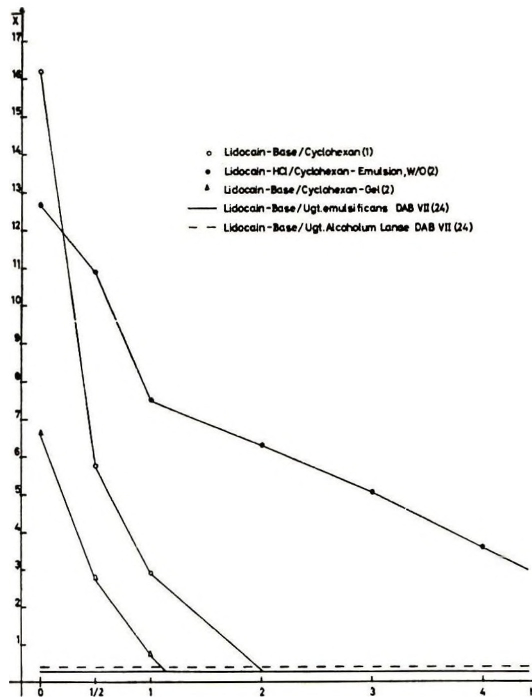

Abbildung 2

Lokalanästhetische Wirkung nach percutaner Aufnahme von 2,5 Gew.-% Lidocain aus verschiedenen Zubereitungen. Applikationsdauer (Stdn.) in Klammern. Abszisse: h = Zeit in Stdn. nach Unterbrechung des äußeren Kontaktes. — Ordinate: x̄ = Faktor der Schmerzschwellenerhöhung.

Die Oberflächenspannung der einzelnen Verbindungen scheint einen limitierenden Einfluß zu haben, der bei etwa 40 dyn/cm liegt. Ähnliches scheint für die Viskosität zuzutreffen. Sie liegt für wirksame Penetrationsvermittler unter 4 cSt. Andererseits kann aus geringer Viskosität natürlich nicht auf gute Penetration geschlossen werden. Das Dipolmoment scheint auch einen Einfluß auszuüben, etwa in dem Sinne, daß eine Hautpenetration bei geringer Ladung eher zu erwarten ist. Aber auch hier gibt es Ausnahmen, z. B. wieder das DMSO.

Nicht eine der untersuchten physiko-chemischen Eigenschaften der Penetrationsvermittler bedingt allein die Hautpenetration. Vermutlich haben wir es mit einer Interferenz mehrerer physiko-chemischer Faktoren zu tun: Zunehmende Viskosität, zunehmende Oberflächenspannung, elektrische Ladung oder Wasserlöslichkeit scheinen die Penetration zu hemmen. Die Wirkung von Penetrationsvermittlern ist grundsätzlich nicht unabhängig von weiteren Inhaltsstoffen einer Zubereitung. Ihre Wirkung wird modifiziert durch Lösungsvermittler, sogenannte Verdicker oder andere übliche Salbeninhaltsstoffe.

Am Beispiel der Lokalanästhesie zeigt *Abb. 2*, wie sehr die galenische Zubereitung eine Wirkung beeinflussen kann. Nach äußerlicher Applikation von

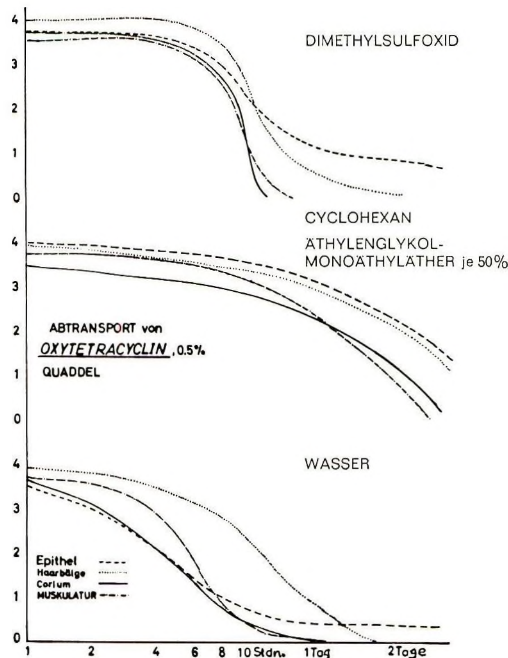

Abbildung 3

Resorptionsgeschwindigkeit nach intracutaner Injektion von 0,5 Gew.-% Oxytetracyclin aus verschiedenen Vehikeln [nach Keesenberg (8)].

zwei üblichen lidocainhaltigen Salbengrundlagen des DAB VII kommt sie nicht zustande. Das entspricht der fehlenden Fluorescenz im Corium nach Anwendung der Tetracyclinsalben (s. *Tabelle 2*). In flüssigen Zubereitungen mit geeigneten Penetrationsvermittlern wird Lidocain dagegen in sicher wirksamer Menge percutan aufgenommen: Die in tieferen Schichten der Haut gelegenen freien Nervenendigungen werden gegenüber Schmerzimpulsen reversibel unempfindlich. Ähnliche — bei Anwendung von Lidocain-hydrochlorid jedoch niedrigere — Effekte lassen sich auch mit W/O-Emulsionen oder Gelen erzielen, wenn diese Penetrationsvermittler in ausreichender Konzentration enthalten. Die percutane Resorption wird mit dem Abtransport aus dem Corium und der Aufnahme in den allgemeinen Kreislauf beendet. Dieser Schritt ist ebenfalls von der Zusammensetzung der äußerlich verabfolgten Zubereitung abhängig. Im Gegensatz zur Penetration der Epidermis scheint hier die vermehrte Wasserlöslichkeit einer Verbindung ihre Verteilung im Corium und die Aufnahmegeschwindigkeit in die Blut- oder Lymphgefäße zu fördern: Sie erfolgt nach Keesenberg (8) aus Wasser rascher als aus Penetrationsvermittlern, aus DMSO schneller als aus einem Kohlenwasserstoff *(Abb. 3)*. Der bei der Penetration der Epidermis eine nur untergeordnete Rolle spielende Wirkstoff kann auf den Abtransport erheblichen Einfluß gewinnen. Werden z. B. Lidocain und Rhodamin B im gleichen Penetrationsvermittler (Cyclohexan und Äthylenglykolmonoäthyläther) zusammen äußerlich appliziert, tritt Lokalanästhesie gleichzeitig mit der Fluorescenz des Farbstoffes im Corium ein. Wenige Stunden später ist die Anästhesie beendet, das Lidocain abtransportiert. Rhodamin B dagegen läßt sich 24 und 48 Stdn. später noch im Corium nachweisen.

ZUSAMMENFASSUNG

Penetrationsvermittler können Wirkstoffe bis ins Corium der Haut transportieren und werden dadurch zu Resorptionsvermittlern. Der Transport bis ins Corium scheint in toto ohne nennenswerte Selektion zu erfolgen. Jenseits der Epidermis verliert der Penetrationsvermittler offenbar seinen Einfluß, und der Abtransport wird zunehmend abhängig vom Wirkstoff. Die percutane Resorptionsgeschwindigkeit kann außerordentlich groß sein. Schon 15 min nach äußerlicher Applikation können Farbstoffe im Corium oder eine Lidocainwirkung nachgewiesen werden. Unterschiede in der Stoffaufnahme zwischen Laboratoriumstieren und dem Menschen sind mit Sicherheit zu erwarten, u. a. auch wegen der Dicke der Epidermis und der Dichte der Behaarung. Schließlich ist auch seit langem bekannt, daß kranke, vorgeschädigte oder alte Haut ihr Aufnahmevermögen für Fremdstoffe ändert. Das Verhalten *in* der Haut kann die intravasale Aufnahme selbstverständlich stark beeinflussen. Es muß auch

auf die mögliche Depotwirkung im Epithel hingewiesen werden. Selbst nach Beendigung des äußeren Kontaktes kann immer noch eine Resorption eintreten. Dies scheint für die Kosmetik wichtig zu sein. Für sie ergibt sich weiter, daß auch in diesem Bereich Penetrationsvermittlung grundsätzlich möglich ist. Manchmal ist sie erwünscht wegen einer möglicherweise angestrebten „Tiefenwirkung". Meistens wird sie es jedoch weniger sein, weil die zwangsläufig eintretende Resorption außer Kontrolle gerät. Ob und in welchem Maße sich Penetrationsvermittler oder die anschließende Hemmung derselben zur Steuerung einer sinnvollen Beeinflussung tieferer Hautschichten heranziehen lassen, muß vorerst offenbleiben. Prinzipiell indessen erscheint es zumindest theoretisch möglich, die Eindringtiefe zu beherrschen. Es ist allerdings oft methodisch außerordentlich schwierig, die erforderlichen Parameter quantitativ zu erfassen. Insgesamt gesehen sollten die technologischen Bemühungen der kosmetischen Forschung mehr noch als bisher durch Tierexperimente ergänzt werden, um auf diese Weise schon frühzeitig auf eine mögliche percutane Aufnahme von Stoffen aus kosmetischen Zubereitungen hinzuweisen oder diese auszuschließen.

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The Influence of pH, Emulsifier, and Accelerated Ageing upon Preservative Requirements of O/W Emulsions

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Synopsis—Twenty-nine individual PRESERVATIVES and 16 combinations of two or more preservatives were tested in an ANIONIC and a NONIONIC OIL/WATER LOTION, each of which was formulated at an acid and an alkaline pH. MINIMUM INHIBITORY CONCENTRATIONS against four representative challenge MICRO-ORGANISMS were determined for the preservatives and/or combinations. Less than 35% of the preservatives or systems tested in lotions were effective. Anionic emulsions were somewhat easier to preserve than formulas made with nonionic emulsifiers.

Introduction

A recent survey by Gucklhorn (1) reviews data on a large number of antibacterial and antifungal compounds. He has gathered information on these compounds from a variety of sources and provides an invaluable review of the pertinent published information. There are, however, serious gaps in available data due to the variation in test methods employed to evaluate the preservatives.

It was our purpose to study those compounds of most interest in a uniform system (or systems). In addition, we were interested in developing a procedure for screening new preservatives that gave more significant results than the traditional serial dilution in broth. Oil-in-water emulsions, known to be highly susceptible to microbial degradation, were chosen as the model systems for this study.

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Representative oil-in-water emulsions were devised to study the following aspects of preservation:

1. Inactivation of preservatives in anionic and nonionic emulsifier systems.
2. The effect of pH on preservation potential.
3. Stability of preservatives upon ageing at elevated temperatures.
4. Determination of Minimum Inhibitory Concentration (MIC) of satisfactory preservatives.
5. Augmentation of activity by inclusion of two or more preservatives.

A survey of the literature on cosmetic preservation shows that several investigators have studied the inactivation of preservatives by nonionic emulsifiers and/or other components of a formulation. Most investigators use an aqueous system to evaluate binding of preservatives by nonionics. Some excellent papers of this genre are by Patel (2), Patel and Kostenbauder (3), deNavarre (4), Wedderburn (5), and Barr and Tice (6).

A number of papers have been published which deal with interactions between anionics and preservatives. Many of these state that anionic emulsifiers may enhance the activity of some preservatives. However, Schuster and Modde (7) demonstrate binding of some preservatives by anionic moieties in aqueous systems.

Entrekin (8) and Wickliffe and Entrekin (9) evaluated the effects of pH on preservatives in a broth medium. Optimal pH conditions were ascertained for 17 preservatives and 4 preservative mixtures.

Oil-in-water emulsions have been used by a few authors to evaluate preservation phenomena. Boehm (10) used emulsions to evaluate synergism between preservatives against a variety of test organisms. Barr and Tice (6) studied the preservation of aqueous solutions containing nonionic surfactants. Those preservatives showing satisfactory results were incorporated into emulsions to compare preservative activity in aqueous systems with emulsions.

The effect of the hydrophilic-lipophilic balance (HLB) of nonionic surfactants on preservatives in emulsions was studied by Tilbury (11). Ten preservatives were incorporated into simple emulsions to evaluate HLB on preservation. Bean *et al.* (12) studied the effects of the partition coefficient of a preservative in cosmetic emulsions.

The present study differs from most of the above investigations in that it is concerned with the simultaneous evaluation of pH, emulsifier type, and accelerated ageing of complete oil-in-water emulsions prepared with the great variety of preservatives now available. Further, it is an extension and updating of several facets of the preservative studies conducted by others. Preservatives no longer usable in cosmetics because of regulatory action have been excluded from evaluation. The authors, instead, have concentrated on those currently available to us including many new compounds with little or no history of use in oil-in-water emulsions. The tables of effective levels

of the various compounds take into consideration not only stability at high temperature but suggest approximate minimum concentrations of preservatives and preservative combinations for oil-in-water emulsions of various types.

Experimental

The test organisms were: *Streptococcus faecalis* (ATCC 4082), *Pseudomonas aeruginosa* (ATCC 15442), *Candida albicans* (ATCC 10231), and *Aspergillus niger* (ATCC 9642).

The bacteria were grown in Trypticase Soy Broth (BBL) for 24 hours at 37°C; the yeast in Mycophil Broth (BBL) for 24 hours at 37°C; the fungus on Mycophil Agar slants for 10–14 days at 30°C. Fungal spores were harvested from 10-day old slants with sterile distilled water and this suspension used for challenge.

Test lotion formulas used in the study are listed in Table I.

Data on preservatives and preservative mixtures tested are given in Tables II–IV. The chemical name, trade name, and source of each of the preservatives are included.

Table I

Formulas for Anionic and Nonionic Test Lotions

Preparations	Acid	Alkaline
Anionic Lotions		
Carbopol 941	0.15	0.15
Cetyl alcohol	0.50	0.50
Glyceryl monostearate, NSE	2.50	2.50
Isopropyl-palmitate-myristate (60-35)	2.00	2.00
Mineral Oil 55/65 SUS	1.00	1.00
Sodium lauroyl isethionate	0.50	0.50
Triethanolamine, 98%	0.05	0.40
Glycerin, anhydrous	4.80	4.80
Water deionized	88.50	88.15
	100.00	100.00
	pH 5.1–5.2	pH 7.9–8.1
Nonionic Lotions		
Mineral Oil 55/65 SUS	20.00	20.00
Cetyl alcohol	5.00	5.00
Span 60	2.50	2.50
Tween 60	7.50	7.50
Sodium phosphate, dibasic, anhydrous	0.01	...
Sodium phosphate, tribasic, anhydrous	...	0.12
Water, deionized	64.99	64.88
	100.00	100.00
	pH 5.4–5.7	pH 7.9–8.3

Table II

Minimum Inhibitory Concentration (%) for Preservatives Effective in One or More Lotions

Preservative		Anionic Lotion[a]		Nonionic Lotion[a]	
Trade Name	Chemical Name	Acid	Alkaline	Acid	Alkaline
Bronopol (Goldschmidt)	2-Bromo-2-nitropropane-1-3-diol	0.05	>0.1[D]	0.1	>0.1[D]
Dehydroacetic acid (Cane's)	3-Acetyl-6-methyl-2H-pyran-2, 4 (3H)-dione	0.1	NT	>0.2	NT
Dioxin = Giv-Gard DXN (Givaudan)	6-Acetoxy-2,4-dimethyl-*m*-dioxane	0.1	0.1	0.15	0.2
DMDMH (Glyco)	Dimethylol dimethyl hydantoin	0.1	0.1	>0.1	0.1
Dowicil 200 (Dow)	Cis isomer of 1-(3-chloroallyl)-3,5,7-triaza-1-azonia-adamantane chloride	0.075[D]	0.1[D]	0.1	0.1
Formaldehyde (Fisher)	Formaldehyde solution, 40%	0.05	0.05	0.075	0.075
Hibitane (Imperial)	Bis (*p*-chlorophenyldiguanido) hexane	>0.1	>0.1	0.1	>0.1
MDMH (Glyco)	Monomethylol dimethyl hydantoin	0.2	0.2	>0.5	>0.5
Nipastat (Nipa)	Nipa ester 82121—mixture of methyl, ethyl, propyl, butyl, benzyl parabens	0.225	>0.3	>0.3	>0.3
Noxyflex (Geistlich)	*N*-Methyl-*N'*-hydroxymethyl thiourea	0.25	0.2	0.5	0.2
Ottasept (Ottawa)	Parachlorometaxylenol	>0.5	0.38	>0.5	>0.5
Phenonip (Nipa)	Mixture of phenoxetol and parabens	0.5°	>0.5	>0.5	>0.5
Phenoxetol (Nipa)	Ethylene glycol monophenyl ether	1.0	1.0	1.0	>1.0
Phenyl ethyl alcohol (IFF)	2-Phenylethanol	1.0	1.0	>1.0	>1.0
Polycide A (Zwicker)	Tris (2-hydroxyethyl) triazonium methyl carboxy phenolate	0.15	0.1	0.15	0.1
Polynoxylin (Geistlich)	Polynoxymethyleneurea	>0.3	>0.3	>0.3	0.3
Sorbic acid (Pfizer)	2,4-Hexadienoic acid	0.1	NT	0.15	NT
Omadine, Sodium (Olin)	Sodium pyridinethione	0.1°	>0.1	0.1°	0.1°

[a] Symbols used: D = Discoloration; NT = Not Tested; ° = Approximate MIC; >*n* = Ineffective at the maximum concentration indicated.

Table III

Minimum Inhibitory Concentrations (%) for Preservative Mixtures Effective in One or More Lotions

Preservative Mixture		Anionic Lotion[a]		Nonionic Lotion[a]	
Trade Name	Chemical Name	Acid	Alkaline	Acid	Alkaline
Bronopol +		0.1°	0.1°	>0.1	>0.1
Omadine, Sodium		0.05	0.05	>0.05	>0.05
DMDMH +		0.1°	0.1°	0.1°	0.1°
Omadine, Sodium		0.05	0.05	0.05	0.05
MDMH +		0.2°	0.2°	0.2°	0.2°
Omadine, Sodium		0.05	0.05	0.05	0.05
Bronopol +		0.018	0.013D	0.005	>0.1D
Methylparaben (Mallinckrodt) +	Methyl *p*-hydroxybenzoic acid	0.038	0.025	0.1	>0.2
Propylparaben (Mallinckrodt)	Propyl *p*-hydroxybenzoic acid	0.009	0.006	0.025	>0.05
Formaldehyde +		0.013	0.018	0.038	0.038
Methylparaben +		0.05	0.075	0.15	0.15
Propylparaben		0.013	0.018	0.038	0.038
Germall +		0.38	0.5	0.5	0.5
Methylparaben +		0.15	0.2	0.2	0.2
Propylparaben		0.038	0.05	0.05	0.05
Germall +		0.5°	0.5°	>0.5	>0.5
Methylparaben +		0.1	0.1	>0.1	>0.1
Butylparaben		0.02	0.02	>0.02	>0.02
Methylparaben +		0.15	>0.2	>0.2	>0.2
Propylparaben		0.038	>0.05	>0.05	>0.05
Hibitane +		>0.1	>0.1	0.1	>0.1
EDTA (Ciba-Geigy)	Ethylene diaminetetraacetic acid	>0.05	>0.05	0.05	>0.05
Vancide 89RE (Vanderbilt) +	*n*-Trichloromethylthio-4-cyclohexene-1,2-dicarboximide	>0.2S	0.075	>0.2V	>0.2V
Phenoxetol		>1.0	0.375	>1.0	>1.0
Preservative 68 (Dutton & Reinisch) +	Halogenated aliphatic amide	0.13	0.19	0.25	0.19
Formaldehyde		0.013	0.019	0.025	0.019

[a] Symbols used: ° = Approximate MIC; D = Discoloration; S = Separation of emulsion; V = Viscosity changes; >*n* = ineffective at the maximum concentration indicated.

Test Procedures

Preparation of Lotions

Test lotions without preservatives were prepared and immediately refrigerated to prevent spoilage. Preservatives were dissolved in water or ethanol,

Table IV

Preservatives and Preservative Mixtures Unsatisfactory in All Lotions Tested

Preservative or Preservative Mixture		Maximum Level Tested (%)
Trade Name	Chemical Name	
Armeen Z (Armour)	n-Coco-B-aminobutyric acid	0.1
Bradosol (Ciba-Geigy)	Dodecyl-dimethyl (2-phenoxy ethyl) ammonium bromide	0.1
Dowicide 1 (Dow)	Orthophenyl phenol	0.2
Dragocid Forte (Dragoco)	Isopropyl sorbate	1.0
Germall 115 (Sutton)	Imidazolidinyl urea	0.5
Omadine, Zinc (Olin)	Zinc pyridinethione	0.1
Parablend (Mallinckrodt)	Mixture of methyl, ethyl, propyl, butyl parabens	0.2
Preservative 68 (Dutton & Reinisch)	Halogenated aliphatic amide	0.5
Propylene glycol (Union Carbide)	1,2-Propanediol	10.0
Tego 103S (Goldschmidt)	15% Dodecyldi (aminoethyl) glycine	0.5
Vancide 89RE (Vanderbilt)	n-Trichloromethyl thio-4-cyclohexene-1,2,-dicarboximide	0.2
MDMH +		0.5
Methylparaben +		0.25
Propylparaben		0.05
Methylparaben +		0.1
Butylparaben (Mallinckrodt)	Butyl p-hydroxybenzoic acid	0.02
Irgasan-Triclosan (Ciba-Geigy) +	2,4,4′-Trichloro-2′-hydroxy-diphenyl ether	0.1
EDTA		0.05
Vancide 89RE +		0.2
EDTA		0.05
Vancide 89RE +		0.2
Formaldehyde		0.05

according to their solubilities and added to 95 ml of lotion in a 4-ounce screw-capped jar. The final volume of preserved lotion was brought to 100 ml by the addition of sterile water, where necessary. After addition of preservative, the lotion was allowed to equilibrate at room temperature for 3–7 days and shaken occasionally. Four 10-ml aliquots were placed in 20 x 150 mm sterile test tubes. The remaining lotion was stored at 52°C for one month, after which time it was re-examined for preservative adequacy.

Challenge of Lotions

Ten-milliliter aliquots of each test lotion were challenged with the following volumes of pure cultures:

Streptococcus faecalis—0.02 ml of 24-hour broth culture (2.7×10^7 organisms/10 ml product)

Pseudomonas aeruginosa—0.02 ml of 24-hour broth culture (3.7×10^7 organisms/10 ml product)

Candida albicans—0.05 ml of 24-hour broth culture (3.5×10^5 organisms/10 ml product)

Aspergillus niger—0.1 ml of a freshly prepared spore suspension (4.5×10^5 organisms/10 ml product)

P. aeruginosa, *C. albicans*, and *A. niger* were recovered in large numbers in all unpreserved test lotions for at least 14 days after challenge. *S. faecalis* survived in high numbers in all lotions except the acid anionic, where no organisms were detected after a 3-day contact period.

Subcultures of Challenged Lotions

At the following time intervals after challenge, each sample was thoroughly mixed and a sterile inoculating loop of *ca.* 0.05-ml capacity was used to streak the lotion onto a Letheen agar (Difco) plate—0 hour, 3 days, and 7 days.

Bacterial and yeast plates were incubated at 37°C for a maximum of 3 days; fungal plates were incubated at 30°C for 3–7 days before discarding.

Storage of Challenged Lotions

Lotions inoculated with challenge organisms were stored at 24°C during the subculture period. After the final subculture, they were discarded.

Stages in the Evaluation of Preservative Adequacy

Freshly Prepared Unaged Lotions—Three decimal dilutions of each preservative were incorporated into each lotion to determine the approximate level of preservative required. The highest concentration tested was usually that recommended by the supplier or noted in the literature; however, in some cases, the maximum level tested was twice the recommended level. Kill or marked reduction of 3 or more challenge organisms within 3 days of inoculation was considered mandatory for additional study. Recovery of high levels of organisms at any preservative level precluded further examination of that level.

Aged Lotions—Samples stored at 52°C for one month were subjected to challenge by the 4 test organisms if they had been proven satisfactory in preservative activity by the previous test. Kill of all challenge organisms within 3 days indicated potentially adequate preservation after storage at elevated temperature. The satisfactory levels determined by the preceding two studies became the starting point for MIC studies. These levels were designated "effective levels."

MIC Studies—Preservatives were incorporated into freshly prepared test lotions in 25% decrements from the "effective level" determined in aged lo-

Table V. Effects of Combining Preservatives on Effective Concentrations and Microbial Spectrum (Individual Preservatives Precede Preservative Mixtures)

	Anionic[a]				Nonionic[a]			
	Acid		Alkaline		Acid		Alkaline	
Preservative	Result	%	Result	%	Result	%	Result	%
Bronopol	S	0.05	U^{c}	0.1	S	0.1	U^{c}	0.1
Sodium Omadine	S	0.1	$U^{s,a}$	0.1	S	0.1	S	0.1
Bronopol +	S	0.1	S	0.1	$U^{c,a}$	0.1	$U^{c,a}$	0.1
Sodium Omadine		0.05		0.05		0.05		0.05
Methylparaben +	S	0.15	U^{s}	0.2	U^{a}	0.2	$U^{s,p,a}$	0.2
Propylparaben		0.04		0.05		0.05		0.05
Bronopol +	S	0.018	S	0.013	S	0.05	U^{a}	0.1
Methylparaben +		0.038		0.025		0.1		0.2
Propylparaben		0.009		0.006		0.025		0.05
Formaldehyde	S	0.05	S	0.05	S	0.075	S	0.075
Formaldehyde +	S	0.013	S	0.018	S	0.038	S	0.038
Methylparaben +		0.05		0.075		0.15		0.15
Propylparaben		0.013		0.018		0.038		0.038
Germall	$U^{c,a}$	0.5	$U^{c,a}$	0.5	$U^{c,a}$	0.5	$U^{c,a}$	0.5
Germall +	S	0.38	S	0.5	S	0.5	S	0.5
Methylparaben +		0.15		0.2		0.2		0.05
Propylparaben		0.038		0.05		0.05	$U^{s,p,c,a}$	0.1
Methylparaben +	$U^{s,c,a}$	0.1	$U^{s,p,c,a}$	0.1	$U^{s,p,c,a}$	0.1		0.02
Butylparaben		0.02		0.02		0.02	U^{c}	0.5
Germall +	S	0.5	S	0.5	U^{c}	0.5		0.1
Methylparaben +		0.1		0.1		0.1		0.02
Butylparaben		0.02		0.02		0.02		0.2
MDMH	NT		NT		U^{c}	0.5	U^{c}	0.5
MDMH +	NT		NT		U^{c}	0.5	U^{c}	0.5
Methylparaben +						0.25		0.25
Propylparaben						0.05		0.05
Vancide 89RE	U°	0.2	$U^{p,c,a}$	0.2	$U^{p,a}$	0.2	$U^{p,a}$	0.2
Phenoxetol	S	1.0	S	1.0	S	1.0	U°	1.0
Vancide 89RE +	U°	0.2	S	0.075	U°	0.2	U°	0.2
Phenoxetol		1.0		0.375		1.0		1.0
Preservative 68	U^{s}	0.5	U^{s}	0.5	$U^{s,p}$	0.5	$U^{s,p}$	0.5
Preservative 68 +	S	0.13	S	0.19	S	0.25	S	0.19
Formaldehyde		0.013		0.019		0.025		0.019

[a] Symbols used: ° = Organoleptic problems; S = Satisfactory; U = Unsatisfactory; NT = Not Tested. Subscript figure denotes survival of: s = S. *faecalis;* p = *P. aeruginosa;* c = *C. albicans;* a = *A. niger.*

tions. The level of preservative was reduced until the minimum inhibitory concentration for the most resistant organism was attained. The level that killed all organisms within 7 days was considered to be the MIC.

RESULTS

Table II summarizes MIC data obtained on preservatives effective in one or more lotions. MIC data for preservative mixtures effective in one or more lotions appear in Table III. Those preservatives and preservative mixtures found to be unsatisfactory in all lotions tested are listed in Table IV.

Organoleptic observations are included and noted as superscripts where applicable. They are explained at the base of the tables. In some cases (notably Vancide 89RE combinations), deterioration of aged lotions prevented further testing of lotions which were initially satisfactory.

In preparing preservative mixtures, the basic approach taken was to combine two or more preservatives so as to eliminate gaps in microbiological spectrum, thereby accomplishing a complementary or synergistic mode of activity for the mixture. Table V presents data which illustrate this approach by comparing preservative activity of each compound when tested alone and when in combination. Only those combinations which show some kind of interaction are presented. Organisms unaffected by the preservative and/or the mixture are indicated by superscripts. Results of mixtures recommended by the manufacturers, such as Germall plus parabens, are also reported in Table V.

Table VI summarizes the results of 174 preservation studies conducted on 4 lotion types. A total of 57 lotions (33%) were adequately preserved. Of these 57 lotions, 33 were anionic emulsions and 24 were nonionic. These results indicate a greater ease in preserving anionic emulsions. Acidic anionic lotions were satisfactorily preserved in 18/44 cases (41%); alkaline nonionic lotions were the most difficult to preserve of the 4 lotion types—10/44 satisfactory (23%).

Table VI

Preservation According to Lotion Type

Lotion Type	Number Tested	Number Satisfactory	Per cent Satisfactory
Acid anionic	44	18	41
Alkaline anionic	42	15	36
Total anionics	86	33	38
Acid nonionic	45	14	31
Alkaline nonionic	43	10	23
Total nonionics	88	24	27
All lotions	174	57	33

Discussion

When a preservative or preservative mixture failed in one or more lotions (Tables II–IV), the failure most often occurred in the unaged lotion. However, in about 30% of the tests, elevated temperature and/or storage for one month appeared to be responsible for loss of preservative activity.

Several combinations of preservatives are effective in one or more lotions by virtue of complementary activity against the test organisms. The combination of Germall with parabens typifies this type of activity. There is also apparent synergism as in the case of Bronopol plus parabens. Some combinations provide partial complementation. EDTA kills *P. aeruginosa* in 3 of the 4 Irgasan-EDTA mixtures tested, but failure to kill all challenge species makes this combination ineffective for any of the lotions. Finally, there is at least one example of apparent antagonism (Bronopol plus sodium Omadine in the acid nonionic lotion). It is obvious that combinations of compounds may provide adequate preservation of formulas in which single preservatives are ineffective. However, one cannot easily predict whether a theoretically acceptable preservative mixture will be effective in a formulation; additive effects,

Table VII

Preservatives Recommended for Various Lotion Types

Preservative	MIC Level (%)			
	Anionic Lotion[a]		Nonionic Lotion[a]	
	Acid	Alkaline	Acid	Alkaline
Bronopol	0.05	NR	0.1	NR
Dehydroacetic acid	0.1	NT	NR	NT
Dioxin (Giv-Gard DXN)	0.1	0.1	0.15	0.2
DMDMH	0.1	0.1	NR	0.1
Dowicil 200	0.075[D]	0.1[D]	0.1	0.1
Formaldehyde	0.05	0.05	0.075	0.075
Hibitane	NR	NR	0.1	NR
MDMH	0.2	0.2	NR	NR
Nipastat	0.225	NR	NR	NR
Noxyflex	0.25	0.2	0.5	0.2
Ottasept	NR	0.38	NR	NR
Phenonip	0.5°	NR	NR	NR
Phenoxetol	1.0	1.0	1.0	NR
Phenylethyl alcohol	1.0	1.0	NR	NR
Polycide A	0.15	0.1	0.15	0.1
Polynoxylin	NR	NR	NR	0.3
Sorbic acid	0.1	NT	0.15	NT
Omadine, sodium	0.1°	NR	0.1°	0.1°

[a]Symbols used: NR = Not recommended; NT = Not tested; D = May discolor; ° = Approximate MIC.

synergism, or antagonism may occur. Experimental evaluation is always necessary.

Our results generally agree with the available literature, i.e., adequate preservation is more easily accomplished in anionic systems than in nonionic systems. Further, acidic conditions allow for the use of a greater number of preservatives than alkaline conditions.

Tables VII and VIII show preservatives and preservative combinations recommended for specific lotion types. The concentrations of preservative given represent the MIC obtained by the various methods employed in this study. Note, that in practice, concentrations higher than the MIC would be employed to compensate for possible loss of preservative due to heat, light, or interaction with other product components.

Table VIII

Preservative Combinations Recommended for Various Lotion Types

Preservative Combination	MIC Level (%)			
	Anionic Lotion[a]		Nonionic Lotion[a]	
	Acid	Alkaline	Acid	Alkaline
Bronopol +	0.1*	0.1*	NR	NR
Omadine, sodium	0.05	0.05		
DMDMH +	0.1*	0.1*	0.1*	0.1*
Omadine, sodium	0.05	0.05	0.05	0.05
MDMH +	0.2*	0.2*	0.2*	0.2*
Omadine, sodium	0.05	0.05	0.05	0.05
Bronopol +	0.018	0.013D	0.005	NR
Methylparaben +	0.038	0.025	0.1	
Propylparaben	0.009	0.006	0.025	
Formaldehyde +	0.013	0.018	0.038	0.038
Methylparaben +	0.05	0.075	0.15	0.15
Propylparaben	0.013	0.018	0.038	0.038
Germall +	0.38	0.5	0.5	0.5
Methylparaben +	0.15	0.2	0.2	0.2
Propylparaben	0.038	0.05	0.05	0.05
Germall +	0.5*	0.5*	NR	NR
Methylparaben +	0.1	0.1		
Butylparaben	0.02	0.02		
Methylparaben +	0.15	NR	NR	NR
Propylparaben	0.038			
Hibitane +	NR	NR	0.1	NR
EDTA			0.05	
Vancide 89RE +	NR	0.075	NR	NR
Phenoxetol		0.375		
Preservative 68 +	0.13	0.19	0.25	0.19
Formaldehyde	0.013	0.019	0.025	0.019

[a] Symbols used: NR = Not recommended; * = Approximate MIC; D = May discolor.

The authors would be guilty of extreme negligence were they not to point out that the data given here cannot be extrapolated to all oil-in-water emulsions. These data were obtained using model systems with relatively low levels of emulsifiers Any significant increase in concentration of emulsifier may require an increase in concentration of preservative or may even contraindicate an otherwise satisfactory preservative or preservative system. Perhaps, to a lesser degree, particular types of anionic or nonionic emulsifiers will also determine whether or not a preservative is effective.

Hence, the "effective" levels of preservatives given in this report should be considered only as a guide to be interpreted according to the particular formulation in question. Following a selection based on types and concentrations of emulsifiers, pH, and other pertinent characteristics of the formula, the suitability of the preservative must be demonstrated by a satisfactory response in a challenge or preservation test (13–15) if the formulator is to be assured of a microbiologically acceptable product.

Finally, the authors wish to emphasize that rather strict standards of acceptance have prevailed in this study, viz., less than 7 days survival at the MIC and less than 3 days at higher concentrations. Although less severe requirements, e.g., a longer survival time or microbiostasis of one or more species, would result in a greater number of acceptable compounds and reduced levels of preservatives in a formula, the strength of the protection against microbial spoilage would be greatly reduced.

ACKNOWLEDGMENTS

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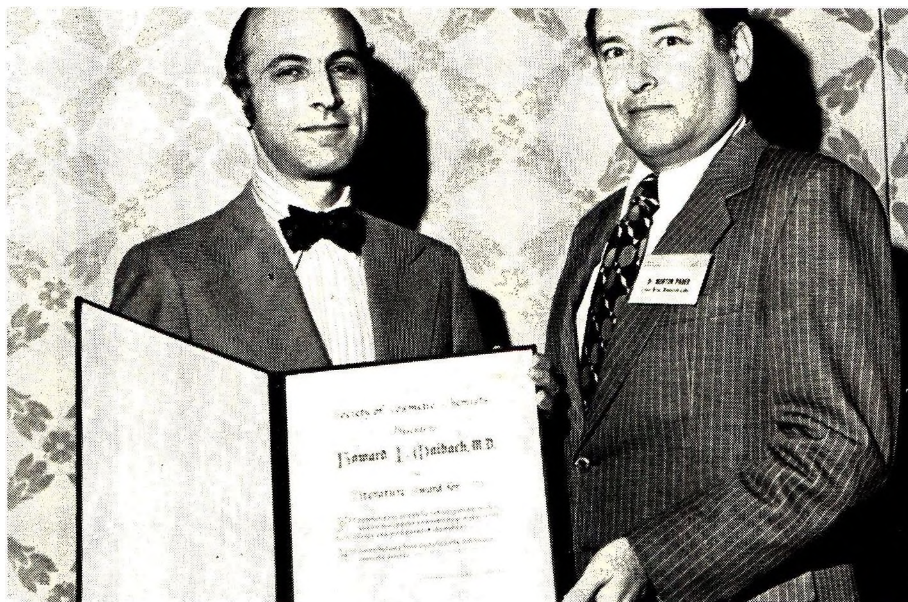
Society of Cosmetic Chemists Literature Award to Dr. Howard I. Maibach

The 1973 Society of Cosmetic Chemists Literature Award was presented to Howard I. Maibach, M.D., Consultant in Dermatology, at the Society's Annual Scientific Meeting held in New York City.

Formal presentation of the award was made to Dr. Maibach by Dr. Hyman Henkin, 1974 President of the Society, during luncheon ceremonies on December 3rd. The award consists of a scroll and an honorarium of $1,500. Dr. Maibach was honored for his research work and numerous publications on dermatology and related subjects.



Left to right: Literature Award recipient Howard I. Maibach and Literature Award Chairman Morton Pader

Book Reviews

McCUTCHEON'S DETERGENTS AND EMULSIFIERS, 1974 ANNUAL, NORTH AMERICAN EDITION, McCutcheon's Division, Allured Publishing Corp., New Jersey, 1974. 248 pages. Price $12.00. Also, 1974 ANNUAL, INTERNATIONAL EDITION. 144 pages. Price $8.00.

McCutcheon's invaluable guides to the world of surface active agents have undergone expansions in 1974 compared to 1973. The North American Edition is about 10% larger, while the International Edition has nearly doubled in length. The modest price increases, $2.00 per volume, are not out of line with those for comparable compendia.

The format of the North American Edition has not changed appreciably from the 1973 Edition. The Experimental Surfactant Section has several new entries, and some of 1973's Experimentals are now found in the main section of the 1974 Edition. With few exceptions there are only sketchy physical and chemical properties noted for the Experimental Surfactants. This lack limits the utility of the Experimental Section.

The listing of surfactants by increasing HLB values which follows the main section is actually a little shorter than the comparable 1973 list. However, an ample selection of HLB values is still presented. The 1974 edition also contains an excellent discussion of HLB followed by a 12-page bibliography of HLB-related references. This new addition, by Paul Becher and William C. Griffin, is a welcome one.

One area where "McCutcheon's" could be improved would be inclusion, wherever possible, of the CTFA Cosmetic Ingredient Dictionary name of each material along with its class and formula.

The International Edition lists products of 98 companies as compared to 89 in 1973, but there are many more individual entries. A correlation between International Trade Names and their North American equivalents would be a useful addition to future editions.

Over the years, McCutcheon's has grown and improved. No practicing cosmetic chemist can afford to be without the current edition close at hand.—EDWARD F. LEVY—Dewey and Almy Chemical Division.

Society of Cosmetic Chemists 1974 Merit Award Presentation

The 1974 Society of Cosmetic Chemists Merit Award was presented to Rosemarie A. Wallisch, Dipl. Chem., consultant to the Cosmetic Industry, LaGrange, Ill., at the December 3rd luncheon during the Society's Annual Scientific Meeting in New York City. The award was given to Mrs. Wallisch in recognition of her many years of outstanding service to the Society. In 1969, Mrs. Wallisch organized the Ohio Valley Chapter and was its chairman in 1970. She was Seminar Chairman in 1974 and is currently a Director of the Society.

Left to right: Merit Award recipient Rosemarie A. Wallisch and Merit Award Chairman Paul Thau

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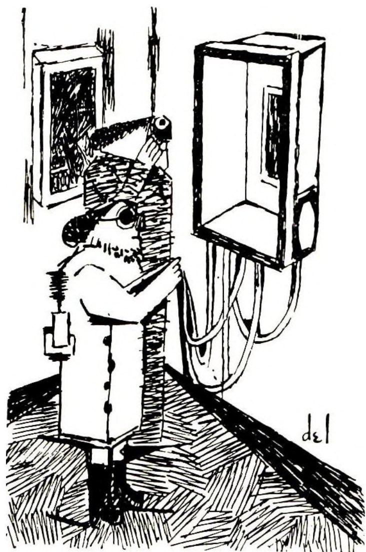

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