

Handbook of Cosmetic Science and Technology

edited by

André O. Barel

Marc Paye

Howard I. Maibach

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André O. Barel

*Free University of Brussels
Brussels, Belgium*

Marc Paye

*Colgate-Palmolive Research and Development, Inc.
Milmort, Belgium*

Howard I. Maibach

*University of California at San Francisco School of Medicine
San Francisco, California*



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Preface

Cosmetic composition and formulation are becoming increasingly complex, and cosmetic ingredients more sophisticated and functional, while laws and regulations impose more constraints on the cosmetic scientist and manufacturer. The *Handbook of Cosmetic Science and Technology* reviews in a single volume the multiple facets of the cosmetic field and provides the reader with an easy-to-access information source.

This handbook covers topics as varied as the physiology of the potential targets of cosmetics, safety, legal and regulatory considerations throughout the world, cosmetic ingredients, vehicles and finished products, and new delivery systems, as well as microbiology and safety and efficacy testing.

To achieve our goal, we, the editors, requested the contributions of expert scientists from academic dermatology and dermato-cosmetics, the cosmetics industry, ingredients and raw materials producers, and regulatory agencies. Because cosmetology is universal, while having some regional specificity, those authors were selected on a broad geographical basis, with some coming from the United States, Europe, Japan, and Australia. They share in their chapters not only their experience and knowledge but also new information and their expert views regarding the future. We thank the authors for their high dedication, which permitted us to make this handbook a review of the state of the art in cosmetology in the new millennium. The staff of Marcel Dekker, Inc., played a great role in the production of the handbook, ensuring on a day-to-day basis the contact between the editors and the authors. Our thanks especially go to Sandra Beberman, Jane Roh, and Moraima Suarez for their constant and excellent help.

Finally, we encourage our readership to send us their comments and suggestions on what should be modified or considered in future editions.

**André O. Barel
Marc Paye
Howard I. Maibach**





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Contributors

Albert Zorko Abram, B.Sc. Soltec Research Pty Ltd., Rowville, Victoria, Australia

Josette André, M.D. Faculty of Medicine, Free University of Brussels, and Department of Dermatology, Hôpital Saint-Pierre, Brussels, Belgium

John E. Bailey, Ph.D. Office of Cosmetics and Colors, Center for Food Safety and Applied Nutrition (CFSAN), U.S. Food and Drug Administration, Washington, D.C.

Robert Baran, M.D. Nail Disease Center, Cannes, France

André O. Barel, Ph.D. Faculty of Physical Education and Physiotherapy, Free University of Brussels, Brussels, Belgium

John Barr, Ph.D. Pharmaceutical Sciences, Advanced Polymer Systems, Redwood City, California

Saqib J. Bashir, B.Sc.(Hons), M.B., Ch.B. Department of Dermatology, University of California at San Francisco School of Medicine, San Francisco, California

Enzo Berardesca, M.D. Department of Dermatology, University of Pavia, Pavia, Italy

Janet M. Blakely, B.Sc.(Hons) Life Sciences Group, Science and Technology, Dow Corning S.A., Brussels, Belgium

Leon H. Bruner, D.V.M., Ph.D. Gillette Medical Evaluation Laboratory, The Gillette Company, Needham, Massachusetts

Stephan Buchmann, Ph.D. Department of Pharmaceutical Technology, Spirig Pharma AG, Egerkingen, Switzerland



Ai-Lean Chew, M.B.Ch.B. Department of Dermatology, University of California at San Francisco School of Medicine, San Francisco, California

William J. Cunningham, M.D. CU-TECH, Mountain Lakes, New Jersey

Rodger D. Curren, Ph.D. Institute for In Vitro Sciences, Inc., Gaithersburg, Maryland

Anton C. de Groot, M.D., Ph.D. Department of Dermatology, Carolus Hospital, 's-Hertogenbosch, The Netherlands

Michel J. Devleeschouwer, Ph.D. Laboratory of Microbiology and Hygiene, Institute of Pharmacy and Biocontaminants Unit, School of Public Health, Free University of Brussels, Brussels, Belgium

Ekong A. Ekong, Ph.D. Technology Division, Hercules Incorporated, Wilmington, Delaware

Joel J. Elias, Ph.D. Department of Anatomy, University of California at San Francisco School of Medicine, San Francisco, California

Peter Elsner, M.D. Department of Dermatology and Allergology, University of Jena, Jena, Germany

Howard Epstein, M.S. Product Development, The Andrew Jergens Company, Cincinnati, Ohio

Paquita E. Erazo-Majewicz, Ph.D. Aqualon Division, Hercules Incorporated, Wilmington, Delaware

Spiros A. Fotinos, B.Sc.(Pharm), B.Sc.(Chem) Corporate Research and Innovation, Lavipharm, Peania Attica, Greece

Bernard Gabard, Ph.D. Department of Biopharmacy, Spirig Pharma Ltd., Egerkingen, Switzerland

Abdul Gaffar, Ph.D. Advanced Technology, Corporate Technology, Department of Oral Care, Colgate-Palmolive Company, Piscataway, New Jersey

Joshua B. Ghaim, Ph.D. Product Development, Skin Care Global Technology, Colgate-Palmolive Company, Piscataway, New Jersey

An E. Goossens, B.Pharm., Ph.D. Department of Dermatology, University Hospital, Katholieke Universiteit Leuven, Leuven, Belgium

Gary Grove, Ph.D. Research and Development, KGL's Skin Study Center, Broomall, and cyberDERM, inc., Media, Pennsylvania



Mary Jo Grove, M.S. KGL's Skin Study Center, Broomall, and cyberDERM, inc., Media, Pennsylvania

Gary S. Hahn, M.D. Department of Pediatrics, University of California at San Diego School of Medicine, San Diego, and Board of Scientific Advisors, Cosmederm Technologies, LLC, La Jolla, California

Allen R. Halper Office of Cosmetics and Colors, Center for Food Safety and Applied Nutrition (CFSAN), U.S. Food and Drug Administration, Washington, D.C.

John W. Harbell, Ph.D. Institute for In Vitro Sciences, Inc., Gaithersburg, Maryland

Jorge Heller, Ph.D. Advanced Polymer Systems, Redwood City, California

Jocélia Jansen, Ph.D. Department of Pharmaceutical Sciences, State University of Ponta Grossa, Ponta Grossa, Paraná, Brazil

Joerg Kahre, Ph.D. VTP Department, Henkel KGaA, Düsseldorf, Germany

Daisuke Kaneko, Ph.D. Department of Product Development, AminoScience Laboratories, Ajinomoto Co., Inc., Kanagawa, Japan

Cees Korstanje, R.Ph., Ph.D. Biological Research Department, Yamanouchi Europe B.V., Leiderdorp, The Netherlands

Alois Kretz, M.D. Cosmetics, Roche Vitamins Europe Ltd., Basel, Switzerland

Hans Lautenschläger, Ph.D. Development & Consulting, Pulheim, Germany

Sabrina Lazzerini, M.D. Department of Dermatology, University of Pavia, Pavia, Italy

Stanley B. Levy, M.D. Department of Dermatology, University of North Carolina School of Medicine at Chapel Hill, Chapel Hill, North Carolina, and Medical Affairs, Revlon Research Center, Edison, New Jersey

Marie Lodén, Pharm.Sc., Dr.Med.Sc. Department of Dermatology, ACO HUD AB, Upplands Väsby, Sweden

John K. Lodge, Ph.D. School of Biological Sciences, University of Surrey, Guildford, Surrey, England

Kate Lusvardi, Ph.D. Aqualon Division, Hercules Incorporated, Wilmington, Delaware

Howard I. Maibach, M.D. Department of Dermatology, University of California at San Francisco School of Medicine, San Francisco, California

Mitsuteru Masuda, Ph.D. Life Science Research Center, Research and Development Headquarters, Lion Corporation, Tokyo, Japan



James K. Maurer, D.V.M., Ph.D. Human and Environmental Safety Division, The Procter & Gamble Company, Cincinnati, Ohio

Mohand Melbouci, Ph.D. Personal Care Department, Aqualon Division, Hercules Incorporated, Wilmington, Delaware

Bozena B. Michniak, Ph.D. College of Pharmacy, University of South Carolina, Columbia, South Carolina

Stanley R. Milstein, Ph.D. Office of Cosmetics and Colors, Center for Food Safety and Applied Nutrition (CFSAN), U.S. Food and Drug Administration, Washington, D.C.

Ulrich Moser, Ph.D. Roche Vitamins Europe Ltd., Basel, Switzerland

Linda P. Oddo, B.S. Hill Top Research, Inc., Scottsdale, Arizona

Louis Oldenhove de Guertechin, Ph.D. Department of Advanced Technology, Colgate-Palmolive Research and Development, Inc., Milbort, Belgium

Rosemarie Osborne, Ph.D. Human and Environmental Safety Division, The Procter & Gamble Company, Cincinnati, Ohio

Gisbert Otterstätter Color Department, DRAGOCO Gerberding & Co. AG, Holzmin-den, Germany

Lester Packer, Ph.D. Department of Molecular and Cellular Biology, University of California at Berkeley, Berkeley, California

Marc Paye, Ph.D. Skin Research Division, Department of Advanced Technology, Colgate-Palmolive Research and Development, Inc., Milbort, Belgium

Alessandra Pelosi, M.D. Department of Dermatology, University of Pavia, Pavia, Italy

Mary A. Perkins, A.Sc. Human and Environmental Safety Division, The Procter & Gamble Company, Cincinnati, Ohio

Véronique Pr  at, Ph.D. Unit   de Pharmacie Gal  nique, Universit   Catholique de Louvain, Brussels, Belgium

Charles Reich, Ph.D. Advanced Technology, Hair Care, Colgate-Palmolive Technology Center, Piscataway, New Jersey

Michael K. Robinson, Ph.D. Department of Human and Environmental Safety Division, The Procter & Gamble Company, Cincinnati, Ohio

Perry Romanowski, B.S., M.S. Research and Development, Alberto Culver Company, Melrose Park, Illinois



Kazutami Sakamoto, Ph.D. Applied Research Department, AminoScience Laboratories, Ajinomoto Co., Inc., Kanagawa, Japan

Claude Saliou, Pharm.D., Ph.D. Department of Molecular and Cell Biology, University of California at Berkeley, Berkeley, California

Subhash J. Saxena, Ph.D. Research and Development, Advanced Polymer Systems, Redwood City, California

Sibylle Schliemann-Willers, M.D. Department of Dermatology and Allergology, University of Jena, Jena, Germany

Mitchell L. Schlossman, B.A., F.A.I.C., F.S.C.C. Kobo Products, Inc., South Plainfield, New Jersey

Uwe Schönrock, Ph.D. Active Ingredient Research, Beiersdorf AG, Hamburg, Germany

Douglas Schoon, M.S. Research and Development, Creative Nail Design Inc., Vista, California

Jörg Schreiber, Ph.D. Research New Delivery Systems, Beiersdorf AG, Hamburg, Germany

Randy Schueller, B.S. Consumer Products Research and Development, Alberto Culver Company, Melrose Park, Illinois

Jørgen Serup, M.D., D.M.Sc. Department of Dermatological Research, Leo Pharmaceutical Products, Copenhagen, Denmark

Ghassan Shaker, M.B.Ch.B., D.Sc. Skinterface sprl, Tournai, Belgium

Kathy Shannon, B.S. Hill Top Research, Inc., Scottsdale, Arizona

F. Anthony Simion, Ph.D. Product Development, The Andrew Jergens Company, Cincinnati, Ohio

Françoise Siquet, Ph.D. Department of Microbiology, Colgate-Palmolive Technology Center, Milmort, Belgium

Klaus Stanzl, Ph.D. DRAGOCO Gerberding & Co. AG, Holzminden, Germany

Dean T. Su, Ph.D. Personal Care, Colgate-Palmolive Technology Center, Piscataway, New Jersey

Takamitsu Tamura, Ph.D. Material Science Research Center, Lion Corporation, Tokyo, Japan



Yoshimasa Tanaka, Ph.D. Life Science Research Center, Lion Corporation, Tokyo, Japan

Roderick Peter John Tomlinson Soltec Research Pty Ltd., Rowville, Victoria, Australia

Rita Vanbever, Ph.D. Unité de Pharmacie Galénique, Université Catholique de Louvain, Brussels, Belgium

René Van Essche, D.V.M., M.B.A. Institute of Pharmacy, Free University of Brussels, Brussels, Belgium

Dominique Van Neste, M.D., Ph.D. Skinterface sprl, Tournai, Belgium

Jürgen Vollhardt, Ph.D. Research and Development, Cosmetic Division, DRAGOCO Inc., Totowa, New Jersey

Elizabeth D. Volz, M.ChE. Research and Development, Colgate-Palmolive Company, Piscataway, New Jersey

Stefan Udo Weber, M.D. Department of Molecular and Cell Biology, University of California at Berkeley, Berkeley, California

Philip W. Wertz, Ph.D. Dows Institute, University of Iowa, Iowa City, Iowa

Ronald C. Wester, Ph.D. Department of Dermatology, University of California at San Francisco School of Medicine, San Francisco, California

Leszek J. Wolfram, Ph.D. Independent Consultant, Stamford, Connecticut

Hongbo Zhai, M.D. Department of Dermatology, University of California at San Francisco School of Medicine, San Francisco, California

Germaine Zocchi, Ph.D. Department of Advanced Technology, Colgate-Palmolive Research and Development, Inc., Milmort, Belgium



Antibacterial Agents and Preservatives

Françoise Siquet

Colgate-Palmolive Technology Center, Milmort, Belgium

Michel J. Devleeschouwer

Free University of Brussels, Brussels, Belgium

INTRODUCTION

The term “antibacterial agent” is largely used to qualify chemical agents that are included in cosmetics or household products to provide them either with a specific bactericidal or bacteriostatic activity during usage. The second function of antibacterial chemicals is to protect the product during its life by providing a preservative efficacy against microbial insults. A particular chemical agent can be used as an active ingredient in antibacterial product or as a preservative to protect the formula from microbial contamination. Taking into account that not only bacteria but also fungi or yeast can be concerned, to cover all germs simultaneously the word “antimicrobial” will be used.

Historically, the first antibacterial products developed were skinwash products such as soap bars, derived from deodorant soap bars. The purpose was not only to clean the skin but also to reduce its microbial flora [1]. During the last 20 years, many different antibacterial or antimicrobial products were marketed. They include toothpastes and mouthwashes, liquid antibacterial soaps, deodorants, and even antibacterial products for dishwashing.

The first part of this chapter will review the different kinds of antibacterial products and the methods to show their efficacy.

The purpose of preservation is to protect all aspects of a product against microbial attack before and during consumer use. Integrity of products in terms of efficacy, fragrance, appearance, and stability must be maintained. The second part of this chapter will review the preservative systems and how to build a well-preserved formula. The test methods for preservative efficacy can be found in Chapter 64 of this book.

ANTIBACTERIAL PRODUCTS

Topical Antimicrobial Products

Most antibacterial soap bars contain triclocarban (TCC) as the active ingredient. In the past, antibacterial soap bars were also formulated with formaldehyde. These were very



effective for hospital use, but skin toxicity and irritation were very high. Currently, liquid soaps are formulated with triclosan up to 1% maximum. Safety of the regular use of triclocarban and triclosan in hand-washing products was extensively discussed by the Food and Drug Administration (FDA) [1]. The agency prepared a tentative final monograph in 1994 in which topical antimicrobial products were classified in the following categories: 1) antiseptic handwash or healthcare personnel handwash, 2) patient presurgical skin preparation, and 3) surgical hand scrub. But this meant that products intended to be used in homecare would have to meet the requirements of products for healthcare. In response, two industrial associations, The Cosmetics, Toiletry, and Fragrance Association (CTFA) and the Soap and Detergent Association (SDA), proposed another classification, based on a healthcare continuum model (HCCM) in which the antimicrobial products were related to six categories; two to be used by the general population (antimicrobial handwashes and bodywashes), three for use by healthcare professionals (presurgical preparation, surgical scrubs, and healthcare personnel handwashes), and one category for food handlers. Since then, industry has submitted data to the FDA showing the efficacy of active ingredients used in the six categories; among these ingredients are triclosan, triclocarban, chloroxylenol (PCMX), povidone-iodine, surfactant iodophor, alcohol, and quaternary ammonium compounds [2].

Extensive studies have also been carried out with essential oils as antibacterial agents in soaps. Unfortunately, the data showed that the minimal inhibitory concentration (MIC) for antimicrobial soaps formulated with different essential oils were more than 100 times higher than the MIC obtained on TCC-based soaps when tested against *Staphylococcus aureus* [3].

Deodorants and Antiperspirants

The first antiperspirants appeared on the market at the beginning of the 20th century. They were based on aluminium chloride, which induced skin irritation and fabric damage because of the low pH of the solutions [4]. Several years later, Shelley and colleagues showed that underarm odor was provoked by the growth of the axillae bacterial flora which degraded the apocrine secretions [5]. These bacteria are mainly staphylococci (*S. epidermidis*) and diptheroids from the *Corynebacteriaceae* family. Antiperspirants can prevent the growth of these degrading bacteria by reducing the available moisture of the axillaries among other mechanisms (see Chap. 56). Some products used the hexachlorophene as an active but its use was discontinued because of its neurotoxic properties [6]. Currently, many contain aluminium salts, or zirconium-aluminium combinations such as Al-Zi-Tri-/tetra-chlorydrex glycinate as active ingredients. Their low pH (4.0) also helps the antibacterial activity. Antiperspirants are deodorants because they suppress the odor source by reducing perspiration and bacterial growth. Deodorants may or may not have an antimicrobial action; either they are masking products—in this case they contain perfumes or essential oils that hide the odor—or they can contain antibacterial agents which are mainly alcohols and triclosan [6].

Oral Care Products

These are mainly toothpastes and mouthrinses. In general, dental creams serve to clean the teeth, to remove dental stains, and most recently to reduce and/or to prevent gingivitis and to kill the germs responsible for bad mouth odor. Mouthrinses, whether their recommended use is before or after brushing, are also claimed to sanitize the mouth.



Active ingredients used in dental cream are mainly triclosan and chlorexhidine. Other ingredients such as the natural sanguinarine extract also claim a sanitizing effect on the oral flora. The same ingredients can be used in mouthrinses, but most also contain alcohol to ensure a good antiseptic effect of the product. It is interesting to observe that fluorinated dental creams without any specific active ingredient also exhibit antimicrobial activity [7]. This could be related to their fluoride content which, in association with the surfactant system in the formula, release antibacterial active cationic systems.

Dishwashing Products

Among the antibacterial household products that have recently appeared on the market, antibacterial hand dishwashing liquids have become increasingly popular. Even if these products are not true cosmetics, during the dishwashing, they are in direct contact with the skin for a certain time. From a safety point of view, they can be considered as rinse-off cosmetics.

Furthermore, some products on the market have a double claim: “dishwashing liquid and antibacterial liquid soap.” They are classical dish liquids based on anionic and non-ionic surfactants, to which one or more antibacterial agents have been introduced. Some of these formula have been optimized to maintain their cleaning/degreasing performance on dishes and to fight bacteria on the hands, in the washing solution, and on washing implements. Ingredients used can be Triclosan, essential oils, or others. The use levels are chosen to ensure a good balance between a maximum efficacy, a low skin toxicity, and keeping good cleaning performances.

Methods to Show Antimicrobial Product Efficacy

In vitro and in vivo tests can be used to show the efficacy of antimicrobial products. Only the in vitro tests will be considered here because they are applicable to all antibacterial products. A detailed review of the in vivo tests, useful for topical antibacterials, can be found in Ref. 1.

—*The minimal inhibitory concentration (MIC) test* principle is to determine the MIC of the test product by performing serial dilutions of the latter in growth medium and inoculating each dilution with the test strain. Products are generally tested at twofold serial dilutions. After suitable incubation, the first tube not exhibiting bacterial growth gives the MIC level, generally expressed in ppm (part per million) of product. The test can be carried out using either 2 mL of broth in tubes or 0.5 to 0.1 mL, in microtiter plates [8] or on agar plates. Control samples without any antimicrobials must be included in the test. This test is very useful to compare activities of different products, products from the same category (e.g., soaps) with different actives, or the active ingredients themselves. However, MIC data obtained on formulated products are very subjective and should be interpreted carefully. Usually, test organisms are *Staphylococcus aureus*, *Staphylococcus epidermidis*, and *Escherichia coli*, for topical antimicrobial. *Pseudomonas aeruginosa* and *Salmonella typhimurium* are added for the dishwashing products; for specific claims in the kitchen, *Aspergillus niger* and *Candida albicans* can be used as test strains. To test oral care products, the chosen organisms are *Actinomyces viscosus*, *Streptococcus mutans*, and *Streptococcus sanguis*, representatives of the oral flora [7].

—*The zone inhibition test* method is largely used to test the resistance of bacteria to antibiotics [9]. Antibacterial agents or products at different concentrations are applied



to a substrate, a paper disk, or directly to the surface of an agar plate previously seeded with the test bacteria. During the incubation, the test product will diffuse into the agar layer and produce a zone of growth inhibition of the micro-organism. The larger the inhibition zone, the higher the efficacy of the product. However, the data are influenced by the diffusion capacity of the product or the active into the agar; oily products will not diffuse at the same rate as aqueous-based products. It is thus very important to use negative and positive controls. The data will be expressed in millimeters of inhibition zone around the disk. The strains used for this test are usually the same that those used for the MIC test. These two methods give a good idea of the bacteriostatic concentrations of the tested product or ingredient.

The requirements from the FDA monograph of 1994 [10] are the MIC test on the active ingredient, the vehicle, and the final formula, associated with a time-kill test methodology to be carried out at several time points over a period of 30 minutes.

—*The time-kill test* determines both the killing kinetics and the activity spectrum of antibacterial formulations. This test is generally performed in suspension. The principle is to place in contact a dilution of the product or the antibacterial agent and a specified bacterial inoculum during a defined period of time. At the end of the contact time, the antibacterial in the mixture is inactivated by dilution into neutralizing broth. Serial dilutions in appropriate broth are performed and the number of survival bacteria enumerated on solid culture media. This method can use different concentrations of test agents and bacterial inocula, and different contact times. In general, the concentrations are chosen so that the final organism/test solution concentration is representative of the use concentration of the product.

In the United States, there is no detailed standardized time-kill test, even if the U.S. Food and Drug Administration (FDA) requested a standard procedure [10]. In response, the American Society For Testing and Materials (ASTM) subcommittee of antimicrobial agents has prepared a draft to standardize the organism inocula, media, neutralizers, and contact times [11].

In Europe, the situation is different: to test the antimicrobial efficacy of products and/or agents, standards exist since more than 20 years in France [12], Holland, Germany, and the United Kingdom. Recently, the Council of Europe has installed a Commission for the Normalization of European Norms [13], which is writing and publishing the European Norms (EN) for testing disinfectants and antiseptics. The requirements for disinfection are 99.99% to 99.999% of killing (4 to 5 log reductions) of the initial inoculum, depending on the test.

These norms are also used by the industry to prove the efficacy of their antibacterial products, but the requirements are less strict: 99 to 99.9% killing (2–3 log reduction). Detailed review of the ENs can be found in Ref. 14.

PRESERVATION AND PRESERVATIVE SYSTEMS

Concept of Active Preservation and Self-Preserving Formula

To ensure effective preservation, the method of choice is to add one or more active antimicrobial ingredients to the product. These ingredients must be compatible with the other ingredients of the formula and must retain efficacy for an extended period of time. They also have to be nontoxic for the consumer.



To choose an active antimicrobial molecule as preservative is not so easy; this molecule must have a good oil-water partition coefficient because the contaminating microbes are living in the aqueous phase of the formula. It must not be inactivated by external factors such as the pH and the manufacturing process [15]. Other factors also have to be considered; such as the packaging, which could affect the preservative activity, the adsorption rate on some components of the formula, the solubility of the preservative molecule and its volatility [15].

Furthermore, the inactivation of the micro-organisms by the preservative should be sufficiently fast to prevent any adaptation or resistance to the preservative system [16]. So, the ideal preservative system must be selected for each formula, taking into account the possible inactivating ingredients or the potentiation capacity of other ingredients. Among these, ethylenediaminetetra-acetic acid (EDTA) is well known to act in synergy with many other chemical preservatives. This potentiation is delivered through the permeation of the cell membrane of gram-negative bacteria. EDTA is a chelating agent and disrupts the outer lipid layer where stability is calcium and magnesium ion dependent. As such, it increases the penetration of the other antimicrobial chemical into the bacterial cell [17,18]. In general, liquid- and emulsion-based cosmetic products are the most susceptible to the development of micro-organisms. Powdered products, such as talc, are also susceptible to contamination and need to be preserved [19].

Another way to preserve a product is to build a “self-preserved” formula by using raw materials that are not supporting germ growing and optimizing their relative content. The use of humectants such as glycerin or sorbitol at a sufficient level increases the formula resistance. In a dental cream, a mixture of sorbitol and glycerine, at respective levels of 10% and 12%, is often enough to protect the formula. This is linked to the decrease of the water activity in the formula because of the presence of these humectants [20]. Other ingredients, such as alcohols, cationic detergents, fragrance components, and lipophilic acids (lauric and myristic acids) used as emulsifiers, which have intrinsically antibacterial properties, can contribute to the self-preservation of a cosmetic. This is also true for essential oils like tea tree oil or geraniol or eucalyptol, often used as cosmetic ingredients.

Some physical factors, such as the pH and the formula water activity, can also contribute to build a self-preserved product. Micro-organisms are essentially living at pH of around 5 to 8, and any pH outside this range induces difficult life conditions for bacteria. The water activity or availability is an important factor as the water is a necessary ingredient for bacterial growth. The water availability concept is detailed in Chapter 64 of this book.

Most Commonly Used Preservatives

Table 1 lists the most commonly used chemicals to preserve cosmetic products. Attention must be paid to the regulations; in Europe, the Annex VI of the Cosmetic Directive 79/768 lists the chemicals, permanently and provisionally allowed to be used as preservatives in the cosmetic products. For each of them, there is an upper concentration use limit, and for several of them, restrictions are mentioned [21]. In the United States, the use of preservative molecules is regulated by the FDA. The chemical preservatives are too numerous to be listed here; details on preservatives can be found in Ref. 22. These molecules can be used in synergistic mixtures to improve the activity spectrum. For example, the parabens can be used with the imidazolydinil urea, the formaldehyde can be used with



TABLE 1 Most Commonly Used Preservatives

Preservative name	Activity spectrum	Compatible with:	Inactivated by:	Optimum pH
Parabens: esters of benzoic acid	fungi, gram+	cationic	anionic, nonionic, proteins	<7
Imidazolydinil urea	broad, weak	anionic, nonionic		4–9
Diazolydinil urea	against fungi	cationic, proteins		
Isothiazolones	broad	anionic, nonionic	bleach, high pH	4–8
		cationic		
Formaldehyde	broad	anionic, nonionic	T° > 60°C	4–9
DMDM hydantoin		cationic		
Benzalkonium Cl	gram+, gram–, weak against molds	nonionic, cationic	anionic, proteins, soaps	4–9
2-bromo-2-nitropropanol, 3-diol	broad	anionic, nonionic	heat, high pH, cysteine, aluminum	<6
		cationic		

Abbreviation: DMDM, dimethyloldimethylhydantoin.

the EDTA, and so on. Most of the preservative manufacturers have developed their own synergistic mixtures of chemicals; this allows them to use lower levels of each chemical and thus decrease the toxicity potential with increased preservative efficacy.

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