PCPC Microbiology Committee

Multifunctionals for the Microbiological Protection of Cosmetics and Personal Care Products

TABLE OF CONTENTS

I. Purpose and Scope

Protecting personal care formulations from microbiological contamination and growth is critical for maintaining both the function and safety for the lifetime of the product. Product function includes formulation stability, delivering an intended and desired effect, and appealing aesthetics. Product safety concerns include protecting the consumer from harmful microbiological contamination and its potential health consequences. Traditionally, preservatives have been used in microbiologically susceptible formulations to ensure product protection. However, the use of traditional preservatives is becoming increasingly restricted by regulatory mandates and public scrutiny. Therefore, alternative and complementary approaches have been gaining widespread use. As a result, multifunctional ingredients have seen growing importance in recent years.

This document is meant to serve as an informational overview for the cosmetic industry by providing a high-level view on ingredients that offer multiple beneficial functions in a formulation, including the ability to support antimicrobial product protection. This document also provides insight into benefits and limitations in formulations for those ingredients classified as multifunctionals. This document attempts to provide clarity and define the terminologies used, as well as other aspects related to the use of such ingredients.

This paper also serves as an informational reference to highlight the key aspects of multifunctionals, including definitions, usage, and their role in formulations. It is not intended to provide comprehensive coverage of the sustainability or other aspects. Instead, it attempts to provide an overview and discuss implications.

II. Definitions

The terms used in this white paper are defined as follows:

Antimicrobial product protection system: The part of a formulation which is responsible for the microbiological control of the formulation. It can be a single ingredient, usually a preservative, or a combination of multiple ingredients, including multifunctionals.

Antimicrobial effectiveness: Antimicrobial effectiveness of a substance or a combination of substances is the ability to prevent the proliferation of microorganisms in a particular application, formulation or ingredient.

FDA: U.S. Food and Drug Administration, the government organization overseeing cosmetics in the United States.

MIC: "Minimum inhibitory concentration" (MIC) is defined as the lowest concentration of an antimicrobial tested that will inhibit the visible growth of a microorganism(s) after incubation.

Multifunctional ingredient (multifunctional): An ingredient that has multiple functions in cosmetics and personal care.
In this paper, we define multifunctionals as cosmetic ingredients which deliver multiple benefits in a personal care formulation, including, as a secondary function, the ability to support in the protection against microbiological contamination.

Preservative: An ingredient added to a personal care formulation specifically to kill and inhibit the growth of microorganisms and which is designated as a preservative by government regulation or trade organization. For the purposes of this paper, “preservatives” are defined as substances in Annex V of the European Cosmetic Regulation No. 1223/2009.[1]

Preservative Efficacy Test (PET): A microbiological test carried out on a personal care formulation to assess the effectiveness of the formulation to inhibit microbiological growth and reduce microbiological count of selected microorganisms over a pre-determined timeframe.

III. Antimicrobial Effectiveness

The goal of antimicrobial protection of personal care products is to control the number of viable microorganisms once the product has been placed on the market. This antimicrobial protection is usually achieved with the help of cosmetic ingredients that support the inhibition of microbial growth or deliver cidal activity against microorganisms. There are many aspects of a cosmetic formulation that influence this ability, such as other ingredients present in the formulation, the formulation type, water activity, % solids, pH, etc.

To determine the antimicrobial effectiveness of formulations, microorganisms (bacterial and fungal) of known quantities are inoculated and monitored for survival at a set interval (often every 7 days) over a set timeframe. This ensures that the antimicrobial action created by the properties of a formulation is sufficient to combat against microorganisms that may be introduced into the product.

This involves using PET methods outlined by organizations such as the International Standards Organization (ISO) [2], the United States Pharmacopeia [3], the European Pharmacopeia [4], the Personal Care Products Council or a method developed internally to meet the company’s needs. However, it is possible to also consider other, faster methods to assess the individual antimicrobial’s activity, such as minimum inhibitory concentration (MIC) [5]. MIC can provide useful information about the general activity of a specific ingredient but is not adequate to get a realistic picture of its performance in a particular formulation due to the complex interactions and combined effect of ingredients present in the formulation.

Multifunctional ingredients may be used to enhance antimicrobial effectiveness. Their role in cosmetic formulations is increasingly important due to the limited options for conventional preservatives arising from regulatory pressure, strict certification criteria, or consumer scrutiny. The same approach used to assess the antimicrobial effectiveness of conventional preservatives can be used when evaluating multifunctional ingredients.

Several key questions need to be examined to help assess the antimicrobial effectiveness of a multifunctional ingredient in the formula, starting with: What is the objective of the multifunctional in a specific formulation? This could include a faster overall kill rate, or synergy with a conventional preservative, allowing for the reduction in the dosage of the traditional preservative, the ability to replace a particular preservative with a safer or more desired alternative or helping to achieve a broader spectrum of protection. A formulation could have challenges with a specific test organism, and the addition of a multifunctional could bring with it a more targeted efficacy against the microbe of concern. Establishing the objective of the multifunctional will help with the selection needed to achieve the specific goal. [6]

Different multifunctional ingredients have different levels of antimicrobial effectiveness. Some may be more effective against bacteria than fungi, or vice versa. Others might primarily target Gram-negative bacteria but display minimal activity towards Gram-positive bacteria, for example. It is important to note that the antimicrobial effectiveness of a cosmetic product is a combined effect of the whole formulation rather than individual ingredients, and that other components of the formulation can also influence the antimicrobial efficacy aside from preservatives or multifunctionals.

IV. Formulating with multifunctionals

While the general considerations for formulating with any ingredient are similar, there are some aspects impacting the efficacy of multifunctionals, including their support of product protection, that are detailed below. [7,8]

1. Use levels (efficacy, impact on formulation properties)

Like any chemical agent, antimicrobial substances have a concentration-dependent antimicrobial effect. While some of them may require use levels in the ppm range to be effective, multifunctionals are typically used at higher, in some cases much higher, concentrations, depending on the particular ingredient and the formulation. Some formulation types are more challenging to protect, such as surfactant solutions, (especially high SPF) sunscreens, or wet wipes, and therefore higher concentrations of the ingredient may be required. [9]

Depending on the multifunctional and the particular formulation, high use levels might impact the esthetics, function, or stability of certain formulations. The safety aspects of the ingredients should also be taken into consideration when a use level is decided. Cost may also be a factor when high use levels are required. [7,9]

2. Order of addition

Multifunctionals may be added at various stages in the process of creating a formulation. The order of addition of any ingredient is determined by factors, such as solubility, temperature stability in relation to the thermal demands of the processing steps, and the potential influence of the ingredient on the formulation, such as emulsion stability and rheology. [10]

If the formulation is made in a hot process, the temperature stability of the ingredient must be considered. Multifunctionals should always be added to the formulation after any process steps that involve temperatures higher than the stability of the multifunctional. When emulsions are prepared at elevated temperatures, multifunctionals are recommended to be added to the cool-down phase. Typically, even in a cold process, these substances are added directly into the water phase or may be added after the emulsion has been formed. Similarly for suspensions, emulsifying agents should always be allowed to coat solid particles before the addition of multifunctionals in order to reduce the risk of the adsorption of the ingredient on the particles.

When the multifunctional ingredient is hydrolytically unstable at the pH level of one of the process steps, this should be taken into consideration. [4,5]

3. pH of the formulation

The pH of the formulation may have three major impacts on antimicrobial efficacy.
1) With hydrolytically less stable chemical classes, such as esters, hydrolysis may take place at acidic or alkaline pHs. For example, esters are considered stable between around pHs 4-8. This must be considered when there are process steps with pH values outside this range. [4,5]
2) Certain chemical classes of antimicrobial substances, such as organic acids or chelating agents, have a pH-dependent effect. Organic acids must be in the protonated, uncharged form in order to be effective. Organic acids have a chemical equilibrium with their negatively charged conjugate bases. This equilibrium gets shifted towards the charged conjugate base as the pH increases, as described by the Henderson-Hasselbach equation.[11] At a high enough pH, determined by the dissociation constant of the particular acid, the relative amount of the neutral protonated form becomes insufficient to provide effective antimicrobial protection support. Generally, using higher concentrations of organic acid may help to make up for the loss of the protonated form, up to a limit set by the maximum use level of the acid.
3) pH may also support antimicrobial product protection by weakening the cell wall of microorganisms. This takes place at acidic or alkaline pHs, having a stronger effect as the pH gets more acidic or more alkaline. This may allow for the use of less efficacious multifunctionals or lower concentrations. [6,7]

4. Single phase vs. multi-phase systems

In a single aqueous phase, water-soluble multifunctionals are simply dissolved, while most water-insoluble materials can be dispersed by first solubilizing them in a water-miscible solvent. The presence of more than one phase creates additional considerations. The hydrophilicity/lipophilicity of the multifunctional determines its partitioning in the two phases. This is particularly a concern for substances with greater lipophilicity. Generally, microorganisms prefer an aqueous microenvironment. Therefore, only antimicrobials present in the aqueous phase have activity against them. With increasing partitioning in the oil phase, less of the ingredient will be available to provide antimicrobial protection. In practice, this may lead to lower overall activity and may require increasing the use concentration of the multifunctional in the emulsion. Additionally, certain multifunctionals may destabilize the emulsification process. In such cases, the use level of the emulsifier may have to be increased to ensure complete and stable emulsification. At the same time, some other multifunctionals may contribute to the emulsification process or the emulsion stability.

For suspensions, particular care must be taken to prevent adsorption of the multifunctionals on the surface of the solid particles, which may result in reduced efficacy. This can usually be achieved by allowing other formulation ingredients to coat the solid particles before the multifunctionals are added and by being considerate of potential incompatibilities. [5,6,7]

5. Solid formulations

Due to the very low water activity, solid formulations are intrinsically unfavorable for microorganisms' growth, hence the formulations require less robust antimicrobial protection. Caution must be exercised, however, particularly with solid formulations that may absorb sufficient water over time to support microbial growth. Therefore, the presence of an antimicrobial protection system, while at lower use levels, is still recommended. Depending on the use concentration and the physical characteristics of the multifunctionals used, such as physical state, viscosity, and sensorial properties, they may influence the texture and sensorial aspects of the formulation. In solid formulations, the solubility and partitioning of the multifunctionals in the small amount of already present or potentially adsorbed water must be considered, since it is only the dissolved or partitioned fraction of the multifunctional that will have activity. [5,6,7]

6. Low water activity liquid formulations

Formulations with lower water activity, such as oil-based formulations, are less prone to microbial growth and require less robust protection. Generally, an environment with a water activity < 0.60-0.70 is not supportive of microbial growth and theoretically does not require protection (ISO 29621:2017). Molds are more tolerant to lower water activity and can reproduce slightly above 0.70, while bacteria require a minimum water activity of 0.81. Therefore, generally lower use levels or multifunctionals with weaker antimicrobial activity may suffice in such formulations, one must consider incidental increases of water activity due to adsorption, humidity, and application environment.

ISO 29621:2017 provides guidelines for the risk assessment and identification of microbiologically low-risk products.[12] Microbiologically low-risk products are defined as
products whose environment denies microorganisms the physical and chemical requirements for growth and/or survival. Such low-risk products may be self-preserving. [4,5]

7. Clear vs opaque formulations

Most formulations are opaque and are more forgiving in terms of ingredient selection, including multifunctionals. Clear formulations require a higher standard of compatibility and true solutions (non-colloidal) of all ingredients in the formula. This may limit the selection of ingredients used, including multifunctionals, and may require adjustments, such as adding a solubilizer. [6,7]

8. Hot vs cold process

Just like other ingredients, the chemical stability of multifunctionals depends on their chemical class. In addition to heat stability, temperature may also play a role in how they can be added to a formulation. Most multifunctionals are suitable for cold process, with a few exceptions. Generally, liquid substances can be dissolved relatively easily, with or without solubilizing agents, at room temperature. In most cases, gentle heating may accelerate the solubilization.

9. Incompatibilities

Several incompatibles are well documented for various types of cosmetic ingredients. Such incompatibilities may result in compromised integrity or stability of the formulation or reduced antimicrobial activity of the product protection system.
Nonspecific physical incompatibilities generally involve solid particles with strong adsorbing power, such as clay materials (e.g., bentonite, kaolin, talc, diatomaceous earth, etc.), cosmetic pigments, lecithin and gums. Adsorption may take place with a broad range of chemical substances, but it’s particularly likely with acidic molecules.

Chemical incompatibilities are generally more specific to particular structural elements. Nonionic surfactants and emulsifiers, such as polysorbate, may interact with organic acids and alcohols. Large amounts of strong binding metal ions may inactivate chelating agents.
On the other hand, certain ingredients, particularly those with some antimicrobial activity, may support the activity of the antimicrobial protection system. Surfactants are an example of such positive influence; however, they may also have a negative influence in some cases by binding certain multifunctionals. [6,7]

10. Solubility

Water soluble multifunctionals can be dissolved in the water phase, be it a single aqueous phase or a bi-phasic system, such as an emulsion. More lipophilic ingredients may require a solubilizer, such as a lower alcohol.

11. Packaging

Packaging may influence the activity of the antimicrobial protection system and may therefore determine the choice of multifunctionals used. The packaging material could have a chemical interaction with formulation components, including multifunctionals. PVC plasticizers, polystyrene, polyurethane, or HDPE may interact with aromatics. Low to medium density polyethylene may absorb some substances. In addition to or instead of a reduction of antimicrobial activity, interaction with the packaging material may have other undesirable consequences, such as the development of odor or discoloration.
Furthermore, one must also consider the choice between translucent and opaque packaging when the multifunctional has some light instability. This is particularly important to consider for aromatics.
Lastly, the packaging configuration should not be overlooked. Certain configurations, such as wide neck containers and refillable packaging are more prone to contamination and microbial growth, and therefore require more robust protection systems, including potentially higher use levels. On the other hand, weaker multifunctionals or lower concentrations may be sufficient for narrow mouth packaging and particularly single use sachets.
The compatibility of the packaging with not only the product protection system but also with the complete formulation as a whole should always be tested to make sure that adequate protection and product quality are maintained. [13]

12. Hurdle technology

The concept of using numerous factors in combination that support inhibiting microbial growth is called hurdle technology. Such factors can be chemical, such as certain ingredients like chelating agents, or physical, such as pH or water activity. Since these factors contribute to antimicrobial protection, their application may allow more robust protection or the reduction of the use level of the antimicrobial substances in the formulation to achieve the same level of protection. The application of hurdle technology may impact how such systems are formulated, depending on which factors are used and to what extent. For chemical factors, when various ingredients are used to support microbial protection, compatibility with the rest of the formulation must be ensured. The order of addition may also have to be considered. For ingredients where the hydrolytic stability or the antimicrobial function is pH-dependent (e.g., organic acids or chelating agents), the pH of the formulation must be maintained within the optimal ranges. [14]

V. Sustainability

Sustainability is a complex concept. It has many aspects that contribute to the overall sustainability profile of an ingredient. Generally, substances with a stronger sustainability profile are more desired. Some of the most important factors that contribute to sustainability are discussed below in relation to multifunctionals.

1. Raw material source

Many cosmetic ingredients, including multifunctionals, are chemically manufactured from petroleum feedstocks. Recently, several multifunctionals have been launched that are marketed as "naturally sourced", "bio-based", "nature-derived" or "green".

Naturally sourced ingredients, in general, are considered to have an improved sustainability profile vs. petroleum-derived ingredients due to the use of renewable feedstocks. However, there are significant differences even between renewable feedstocks that may impact sustainability. A raw material obtained by upcycling a waste product may be highly desired from a sustainability perspective. An example is ingredients derived from bagasse, a waste product of the sugar industry. Upcycling not only creates value from otherwise discarded waste but also allows for the reduction of waste and for better utilization of natural resources.

Plant-based substances may come from various different sources, and the sustainability is strongly dependent on the particular plant. For example, palm oil-based ingredients may be less sustainable unless they are derived from RSPO (Roundtable on Sustainable Palm Oil) grade palm oil. Recent advances in new multifunctional ingredients have seen the rise of the castor bean plant as a highly sustainable raw material source. A resilient plant well suited for cultivation in marginal lands inadequate for food crop cultivation, with several harvests a year, is the kind of ideal feedstock that creates income for farmers without taking fertile soil away from food crops or causing deforestation.

The above aspects do not constitute an exhaustive list. Many other factors including region, water requirements, local agricultural practices, fertilization, etc. also play crucial roles in assessing the sustainability of a raw material and should be considered when determining a material's overall sustainability profile.

2. Production process

Unless the ingredient is a plant extract, there are multiple steps of chemical transformation involved in the production process of creating a multifunctional from a plant. This process itself can have varying degrees of sustainability, which can be influenced by factors such as:

a) Adherence to the Principles of Green Chemistry
b) Energy utilization
c) Water consumption
d) CO_2-generation
e) Social impact
f) Waste

Some of these factors are included in the Life Cycle Analysis (LCA) of a product.

3. Biodegradability

Many cosmetic ingredients, including some traditional preservatives are unable to be fully degraded and residuals have been reported to reside in both the human system [15] and in the environment [16]. Biodegradability reduces the risk of bioaccumulation and is therefore more sustainable for the environment. "Inherently biodegradable" is defined to have a biodegradability of >20% and <60% within 28 days according to OECD 301A-F. [17] "Readily biodegradable" is defined as >60% biodegradable within 28 days according to OECD 301A-F. Since biodegradability is determined by the chemical composition of a substance, it's specific to the individual material. Most Multifunctionals are usually either inherently or readily biodegradable.

4. Certifications

Various certifications exist to attest to the sustainability or renewable feedstock origin of ingredients or finished formulations. The certification processes and the criteria vary. Some of the most well-known certifications include:

a) NaTrue (www.natrue.org): A certification based on the feedstock and the chemical transformations
b) COSMOS (www.cosmos-standard.org): A certification based on feedstock, chemical transformation, and environmental toxicity.
c) USDA Biopreferred (www.biopreferred.gov): A certification involving radioisotope testing of biological carbon content.
d) RSPO: A certification system providing a global standard to ensure the credibility of palm oil sustainability claims and improve the quality of life of palm oil farmers.
e) Bonsucro: A certification program that aims to promote sustainable sugarcane production and trade by ensuring fair labor practices and environmental protection in the sugarcane industry.

5. Inherent sustainability

Multifunctionals have the potential to replace several ingredients at the same time by fulfilling their role in the formulation via their multiple functions. Therefore, they reduce the number of ingredients required for a formulation and hence they inherently represent more sustainable options compared to single-function ingredients.

VI. Conclusions

As preservatives are becoming regulated more strictly, fewer options are available to formulators to utilize. Multifunctionals can support formulators in creating new product protection systems, while also taking advantage of the other functions these ingredients bring to the formulation. [18] The evolving demands in the cosmetic industry for non-controversial and reliable solutions, changing regulations and strict certification guidelines highlight the need for suitable multifunctional ingredients that support efficient antimicrobial protection while meeting consumer expectations for safe products. Multifunctionals, defined as components that offer multiple benefits within a formulation broaden the range of available options. Their efficacy must be verified and their application must be handled with similar considerations to other cosmetic ingredients.

VII. References

[1] Annex V, EU Cosmetic Regulation 1223/2009, https://echa.europa.eu/cosmetics-preservatives

[2] ISO 11930:2019, Evaluation of the antimicrobial protection of a cosmetic product

[3] USP, 2019: United States Pharmacopeia, USP <51> Antimicrobial Effectiveness Testing, 2019.

[4] European Pharmacopeia, EP 5.1.3 Efficacy of Antimicrobial Preservation. European Directorate for the Quality of Medicines & Health Care, 2019.

[5] *Andrews, J. M.* Determination of minimum inhibitory concentrations, J. Antimicrobial Chemotherapy, **48** (2001), 5-16.

[6] *Fiorentino, F. A. M., Chorilli, M., & Salgado, H. R. N.* The use of the challenge test to analyze preservative efficiency in non-sterile cosmetic and health products: applications and critical points, Analytical Methods, **3** (2011), 790-798.

[7] *Draelos, Z. D.* Cosmetic Dermatology: Products and Procedures. Wiley-Blackwell, 2012.

[8] *Geis, P.A.* Cosmetic Microbiology: A Practical Approach, Taylor & Francis, 2006.

[9] *Siegert, W.* Sustainable Use of Preservatives in wet cleaning wipes, Household and Personal Care Wipes, Fall 2012, 26.

[10] *Barel, A.O., Paye, M., Maibach, H.I.* Handbook of Cosmetic Science and Technology, CRC Press, 2009.

[11] *Po, H. N., Senozan, A.* The Henderson-Hasselbach Equation: Its History and Limitations, J. Chem. Ed. **78** (2001), 1499.

[12] ISO 29621:2017. Cosmetics — Microbiology — Guidelines for the risk assessment and identification of microbiologically low-risk products, International Organization for Standardization, 2017

[13] *Halla, N., Fernandes, I. P., Heleno, S. A., Costa, P., Boucherit-Otmani, Z., Boucherit, K., Rodrigues, A. E., Ferreira, I. C. F. R., & Barreiro, M. F.* Cosmetics preservation: A review on present strategies, Molecules, **23** (2018), 1571.

[14] *Ballamwar, K., Sahasrabuddhe, S. D., & Chafle, K.* A Review: The hurdle technology - Self-preservation technology in cosmetics, Int. J. Sci. Res. Pub. **10** (2020), 820.

[15] *Scattergood, G*. Preservatives in skincare products may negatively affect cells via impact on collagen: New study, Cosmetics Design Europe (2023).

[16] *Penrose, M.T., Cobb, J.P.* Identifying potential paraben transformation products and evaluating changes in toxicity as a result of transformation, Water Environ Res. **94** (2022), e10705.

[17] OECD301A-F, 1992, https://www.oecd-ilibrary.org/

[18] *Juncan, A. M., Rus, L. L., Craciun, V. I., & Tincu, A. L., Morgovan, C.* Application of a multifunctional additive in cosmetic preparations for safe preservation. Revista de Chimie, **70** (2019), 2429.