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HURDLE TECHNOLOGY: ARE BIOCIDES ALWAYS NECESSARY FOR PRODUCT PROTECTION ?

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Summary

This new preservative system approach for product protection includes compounds (Hurdles) that have multi-fuctional activity and packaging components that may contribute directly or indirectly to keeping the environment hostile to microorganisms. Preservative-free or self-preserving formulas offer numerous advantages. This approach to product preservation helps reduce and/or eliminate chemical preservatives which are a major cause of skin irritation or contact sensitivity. Self-preserving products reduce the costs of using classical chemical preservatives, meet the demands of a growing segment of consumers who demand natural products, encourage the use of contamination-resistant packaging and allow the use of global formulas without the usual regulatory issue surrounding preservatives. The principle of Hurdle technology provides a scientific basis for developing preservative-free or self-preserving products.

Riassunto

Questo nuovo approccio (Hurdle Technology) al modo di preservare i prodotti cosmetici include l'uso di composti che svolgono un'attività pluri-funzione e componenti del "packaging" che possono contribuire direttamente o indirettamente a mantenere l'ambiente ostile nei confronti dei microrganismi.

Formule prive di conservanti o che si auto-conservano offrono molti vantaggi.

Questo nuovo approccio aiuta a ridurre o ad eliminare completamente l'uso di conservanti chimici che rappresentano la causa maggiore di irritazione o di sensibilità cutanea.

Con i prodotti che si auto-conservano viene ridotto il costo per l'uso dei classici conservanti chimici, viene data una risposta ai consumatori che desiderano acquistare prodotti naturali, viene incoraggiato l'uso di formule globali prive di conservanti.

Il principio attivo della tecnologia "hurdle" pone le basi scientifiche per lo sviluppo di prodotti privi di conservanti e auto-conservabili.

INTRODUCTION

The year 1910 was important to the history of medicine since the drug 606 Salvarsan proved to be the "Magic Bullet" which Paul Ehrlich discovered for the treatment of syphilis. This discovery caused Western medicine to seek "Magic Bullets" for man's other illnesses. The belief that there was a single "Magic 8ullet" for curing disease avoided the notiori that trhere was any benefit of remedies which were complex in nature. Herbal medicines which were the bases of older forms of medicirle and the philosophy (the whote is greater than its palts) for their use was not held in high regard by Westem scientists. Western and Eastern medicine with time grew further and further apart. The wonderful results found for "Magic Bulets" in Western medicine was carried to other disciplines including the preservation of cosmetic and drug products. Here the "Magic Bullet" was formaldehyde. Overtime the limitation of this and other "Magic Bullets" used for product preservation became obvious. The search for new, safer, or more effective preservatives is discouraged by the cost and time required--not only for local registration, but for testing and registration to meet global regulatory requirements. There is general agreement now that no single chemical is able to fulfill all the universal requirements for product protection. To overcome tkis problemJ many preservative suppliers are blending well-established germicides to develop cost-effective systems with broad-spectrum antimicrobial action. While these blends are able to reduce the amounts of preservatives needed in some instances, they fail to deal with current medical concerns of skin sensitivity, environmental issues and perceived health benefits of "preservative-free" products.

Opportunities exist for innovative formulators who want to look beyond current technologies and apply new principles of preservation to the development of novel preservative-free and/or self-preserving products. Consumer and environment- friendly products ean be made without preservatives but this may require modification of current formulations and packaging. The application of Hurdle Technology to cosmetic and drug preservation is critical to making safe and effective prnducts. This technology combines a number of preservative factors (hurdles) that the microorganism(s) in question are not able to survive ("jump over"). Homeostasis of a microorganism is a requirement of the organism to maintain a stable and balanced internal environment. Preservative hurdles can disturb this equilibrium. If the hurdles are high enough or numerous enough, they will prevent the microorganism from multiplying causing them to remain inactive or even to die. Using an array of inhibiting factors (water activity, pH, surfactants, fatty acids and esters, packaging,etc.) allows less extreme use of any particular preservative treatment, especially classical preservatives, to control microbial growth. Such products can be labeled "preservative-free" or more accurately "self-preserving". An important aspect of Hurdle Technology is that the different hurdles mentioned above may result in synergistic rather than simple additive effects. This is an example of how the whole (Eastern science) is larger than the sum of its parts (Western science). In the following pages the influence of various hurdles on microorganisms will be described and how this may lead to preservative-free or self-preserving products without compromise of present microbial standards.

WATER ACTIVITY(a_W) AND PH

Living organisms have water as an absolute requirement for survival and growth. Control of microbial growth can usually be carried out by limitins the availability of water. This becomes easier to understand when the water requirements of the microorganism are known, and these are:

A. Each microorganism has a characteristic optimal a_w and its own range of a_w for growth for a given set of environmental conditions.

B. The a_w requirements of microorganisms are affected by the kind and levels of solutes present, the nutritional value of substrates avaiable, temperature, pH, and other factors in the formula.

C. An unfavorable a_w will increase the lag time and decrease the rate of growth.

D. Bacteria generally have higher a_w requirements than yeasts; yeasts generally have higher a_w requirements than molds.

The a_w of a formulationl may be reduced by the addition of water-soluble solutes including salts,polyols (e.g., glycerol, propylene glycol, glucose), protein hydrolysates, and aminoacids. Table 1 shows the lowest a_w values permitting growth of microorganisms important in contaminated cosmetic products.

It is evident that addition of water-soluble solutes (saits, polyols, short-chain fatty acids, etc.) that lower the a_w to less than 0.95 will prevent the growth of gram negative bacteria comparable to pseudomonads (Pseudomonas aeruginosa and P. fluorescens), coliforms (Escherichia coli) and Salmonella sp. Similarly, addition of solutes that decrease the a_w to less than 0.86 will prevent the growth of virtually all gram positive and gram negatives bacteria that may cause problems in cosmetics and drug formulations.

Microorganisms of interest to the cosmetic and pharmaceutical industries are generally aerobic and have pH optima (pH 5-8) for survivability. The pH requirements of typical spoilage microorganisms are listed in Table 2.

The growth rate of microorganisms generally decreases as the pH departs from neutrality or from the optimum pH for growth for each organism.

Table I

Lowest a_w permitting growth of microorganism.

Class of Microorganism	Minimum a_w Value
Pseudomonads	0.97
Coliforms	0.95
Staphylococcus aureus	0.86
Yeasts	0.88
Molds	0.80

Table II

pH requirements of typical spoilage microorganisms

Class of Microorganism for Growth	Typical pH Range
Some Bacteria (Pseudomas sp.) and Some Molds	pH above 8.0
Many Bacteria (Gram Positive, Gram Negative, Spore-Formers)	pH 5.0-8.0
Lactobacilli; Yeasts ard Molds	pH 3.5 - 5.0
Yeasts and Molds	pH below 3.5

Although many yeasts and molds are able to tolerate acid pH conditions (i.e., pH <4.0), many microorganisms are metabolically injured or stressed by extreme pH conditions--where the pH is <4 or >10. One needs to avoid extreme pH alone in creating a hostile environment because excess acidity or alkalinity may make some products harsh or irritating--especially leave-on products. However, use of specific acidulants (e.g.citric acid, lactic acid; phosphoric acid) to decrease the pH to <5, or use of alkaline materials (e.g., NaOH, triethanolamine) to increase the pH to >9, will make the product more difficult for many microorganisms to grow.

The use of unfavorable acidity or alkalinity (low or high pH) can be a part of a product's preservative system. The class of acidulants used is also important. As an example, lactic acid ean not only lower the pH but also act as a chelating agent.

Chelators enhance the potency of a product's preservative system as will be shown later in this paper.

SURFACTANTS IN SELF-PRESERVING FORMULAS

The primary use of surfactants is as detergents, foaming or wetting agents, solubilizers or dispersants. Surfactants also act as co-emulsifiers because they are partly water soluble and partly oil soluble. This hydrophilic-lipophilic balance (HLB) is a function of specific structure and temperature.

Surfactants are classified as anionic, cationic or nonionic. When present in aqueous solutior at concentratiorls above their critical micelle concentration (CMC) surfactants can form micelles. Preservatives absorbed or enclosed in micelles have decreased preservative efficacy due to a reduction in preservative concentration. Surfactants on the other hand may help solubilize preservatives thereby making them more effective.

Surfactants such as fatty acid soaps are the earliest example of an anionic compound helping preserve products These anionic surfactants have weak antibacterial effects ander alkaline conditions and generally are more active against gram positive rather than gram negative organisms. The general resistarlce of gram negative organism is due to the protection afforded by their outer membrane. This protection can be lowered or reduced by the concurrent use of chelating agents (see Chelating Agents).

Cationic surfactants ionize in aqueous solution to produce positively charged organic ions that are responsible for surface activity. Sirce 1935 when Domagt identified the antimicrobial effects of cationic surfactants, quaternary salts have been used in sanitizers, cosmetics, mouthwashes and toothpastes. Benizalkorium chloride (BAC) and cetyl pyridinium chloride (CPC) are most often used in such formulations. Their presence reduces and / or eliminates the need for additional preservatives. One advantage of quats are their broad spectrum of antimicrobial activity over a range of pH values.

Surfactants are classified as nonionic when they do not ionize in aqueous solution. As a general rule nonionic are not intrinsically antimicrobial. Used below their CMC these agents lower interfacial tension and may make microorganisms more susceptible to biocides. Ethoxylated (EO) or propoxylated (PO) nonlonic surfactants generally inhibit lipophilic germicidal activity and should be avoided. The only exception are block polymers (Pluronics) which do not inhibit lipophilic germicides. Surfactants that are classified as ampholytic can be influenced by pH to give species that have characteristics of either an anionic or a cationic surfactant. The two main types of amphoteric surfactants are the cyclic imidazolines and substituted betaines. Synergy has been shown where mixtures of long-chain betaines and quats were used against gram-negative organisms, however, there was a loss of activity against gram-positive bacteria which is unusual.

FATTY ACIDS AND ESTERS AS MULTIFUNCTIONAL COMPONENTS

Fatty acids have a long history of uses as antimicrobial and anti-insecticidal agents. The earlier successful uses in these areas were diminished with the ability of organic chemists to develop more lethal "Magic Bullets". These chemical advances came with a price of increase toxcity and added environmental problems. Fatty acids are now used in formulations primarily as acidulants, co-emulsifier or super-fatting agents. As antimicrobial agents their action results from the undissociated molecule rather than the anion. Because of this the antimicrobial activity of soaps is profoundly affected by pH. Greater activity can be found at lower pH.

While monoglycerides have been widety used in cosmetic, they represented a mixture of mono-, di and triesters.

The usual cosmetic grades of glycerol monostErate (GMS) have a monoester content of 40-45%.

The more highly purified monoglyceride (>90%) monoester behaves differently than the usual commercial grade. Distilled monoglycerides form emulsions which have small and uniform particle size leading to more stable and more easily preserved emulsions. Where the fatty acid is changed to medium-chain (C_8 -C_{12}) isomers, an added benefit of germicidai action has been found. Monolaurin (Lauricidin®), produced by Med-Chem Labs, Galena, Illinnos (U.S.A.) has been shown to be the ester of choice. It not only helps emulsify a system, create a hostile environment but has very good emolliency for the skin.

This monoester is a wonderful example of finding new uses for an old chemical family by simple changes in their composition and purity.

BIOMIMETIC PHOSPHOLIPIDS

Phospholipds are another example of emulsifiers which can have special properties. While some phospholipids (lecithin) can inactive preservatives, lipids which mimic structure and function of phospholipids have been prepared that have antimicrobial activity. This new family of phospholipids has been developed in which the arrangement of the phosphate and quaternary groupinqs has been reversed. Rather than interfering with preservative systems the biomimetic phospholipid display potent antimicrobial activity without showing significant toxicity or skin irritation efects.

These new lipid derivatives are active against a wide spectrum of organism and have minimun inhibitory concentrations (MIC) between 50 and 1250ppm.

ANTIOXIDANTS AS PRESERVATIVES

Although the primary function of antioxidants is to delay autoxidation of unsaturated lipids in products, they also show significant antimicrobial activity. This function is apparent from their structure. Primary antioxidants are phenolic compound. Butylated hydroxyanisolsole (BHA) Butylated hydroxytoluene (BHT), tertiary butylhydroquinne (TBHQ) and propyl gallate (PG) are the most common phenolic used in cosmetics. BHA and TBHQ are the most effective antimicrobial of the phenolic antioxidants and are most active than the usual parabens. Although, most effective against gram posiive organisms, these phenolics are active against certains gram negative organisms as well as molds and yeasts.

The choice of antioxidant depends on the ease of corporation, composition of the product, the order of addition and packging. Safety, compliance with governmental regulatins and cost should be considered. The final selection of the "hurdles" to be used in a preservative system depends on the specifics of the formula, the manufacturing process and the end-use by the consumer.

AROMA CHEMICALS AS PRESERVATIVES

Spices and essential oils have long been used to prevent the deterioration of products. Shen Nung, a Chinese emperor neariy 5OOO years ago, was responsible for the first known herbals. Aromatic substances have long been used in one form or another to combat disease. Because most studies for evaluating essential oils and fragrances used agar streak or disk method, the true efficacy of many extracts were not properly evaluated. Despite these short comings the antimicrobial properties of aromatic substances were found to be useful. Table 3 gives the phenol coefficient of a number of essential oils.

Table III

Phenol Coefficient of Essential Oils

Essential Oil	Phenol Coefficient
Oil of Clove	9
Oil of Thyme	15
Oil of Cinnamon	9
Oil of Rose	6
Oil of Lemon	4
Oil of Eucalyptus	4
Oil of Lavender	5

Tne active principles in aromatic oils include alcohol, aldehydes, acids, phenols, esters, terpenes, and polyphenols. Aroma chemicals are multifunctional so that their use in products should not only be based on the desired scent but also upon its inherent germicidal properties.

CHELATING AGENTS AS PRESERVATIVES POTENTIATORS

Chelating agents like ethylenediaminetetraacetic acid (EDTA) have been used since the late1930's. While originally developed to counteract the deleterious effects of the hard water on quats, they have been found to potentiate the effectsof biocides. Although EDTA and other chelating agents are considered weak biocides, their effects as biocide potentiators are significant. The antimicrobial benefets of chelating agents were reported by Repaske in 1958. In the same year MacGregor and Elliker demonstrated that EDTA exerts a lytic action on the outer lipopolysacchride layer of the walls of gram-negative bacteria. Under these conditions gram-negative organisms tends to react more like a gram-positive organism and are easier to kill. The greast potentiating effect is found on Pseudomonas sp. EDTA is not the only chelating agent that can be used. Acidulants such as citric, lactic and polyphosphoric acids have chelating ability and also show potentiation of preservative action by acting as acidulants.

PACKAGING & PRODUCT PRESERVATION

If the use of preservative-free or self-preserving formulas are to be realized, then the applicationof the better protective packaging must be considered a hurdle. Inclusive in this concept is the use of delivery devices which do not allow contamination to occur during use.. Flip-caps for shampoos and pump-tops for lotions are example of containers that help reduce contaminatin,, during in-use conditions. While single-use containers are an obvious solution to the problem, other more imaginative solutions are being developed. Some companies are already marketing products without preservatives in containers that can dispence product without contamination.

HURDLE TECHNOLOGY

This new preservative system approach for product protection includes compounds (Hurdles) that have multi-fuctional activity and packaging components that may contribute directly or indirectly to keeping the environment hostile to microorganisms. Preservative-free or self-reserving formulas offer numerous advantages. This approach to product preservation helps reduce and/or eliminate chemical preservatives which are a major cause of skin irritation or contact sensitivity. Self-preserving products reduce the costs of using classical chemical preservatives, meet the demands of a growing segment of consumers who demand natural products, encourage the use of contamination-resistant packaging and allow the useof global formulas without the usual regulatory issue surrounding preservatives. The principle of Hurdle technology provides a scientific basis for developing preservative-free or self-preserving products.

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