Feature: Preservatives 2004
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> ***EU Cosmetics Directive (76/768/EEC)***
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> *Preservative: " a substance which may be added to a cosmetic product for the primary purpose of inhibiting the development of microorganisms in such products ….*
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> *In addition, a preservative must not materially affect the product and must be safe in use"*

When the formulating chemist receives a new product development brief any reference to preservatives is likely to be negative as the marketing department responds to consumer fears, however ill-founded. Add to this the need for universal acceptance of the chosen system in world-wide markets, product compatibility, preservative stability and period after opening (PAO) requirements and the need for designing the preservative system from the outset as an integral part of the formulation instead of adding it almost as an afterthought becomes all too apparent.

Consumer fears fuelled by misunderstandings, poor science and malicious gossip in the tabloid press and on the internet have created problems for the parabens, which are the preservatives of choice for the majority of personal care products. Dene Godfrey, SPC April 2004, gave an excellent and well-reasoned opinion that discounted claims that parabens caused breast cancer. In the same issue Dr Chris Flower, Director General, CTPA, supported the argument in favour of parabens made by Godfrey and criticised the rush to publication with unsupported data by certain publicity seekers and the harm that this causes to the scientific community at large.

Godfrey is Sales and Technical Director of MGS Micropure, a relatively new company that specialises in the supply of preservatives under its Paratexin brand to the personal care industry. The extensive Paratexin range is supported with a full in-house microbiological testing service and the company offers close collaboration with its customers in developing an effective preservation strategy, which optimises preservative use and minimises costs.

There are 143 materials listed as approved preservatives in the European version of the INCI Directory of Cosmetic Ingredients, last updated in September 2003. This would appear to be plenty but it includes a number of quaternary ammonium salts more commonly used as hair conditioning aids and with limited compatibility in other products. The list shown in Annex VI, Part 1 of the European Directive, Spring 2004, as preservatives shows 53 permitted materials or material groups, all subject to restrictions on concentration and many to areas of use. The Table, kindly supplied by Chris Cairns, Schulke & Mayr UK, lists the more commonly used cosmetic preservatives and shows their strengths, weaknesses and mode of action.

Preservative	Strengths	Weaknesses	Mode of action
Benzoates / Sorbates	Low Toxicity Food approvals Global approvals	Active only pH 4-6 Incompatible with cationics and some non-ionics	Protein denaturation May interfere with active transport across cell membrane
Benzyl Alcohol	Global approval Good against Gram negative and Gram positive bacteria	Inactivated by non-ionic surfactants	Membrane disruptor
2-Bromo-2-Nitropropane-1,3-Diol (Bronopol)	Good bactericide Favourable toxicological profile	Concern over nitrosamine formation in presence of secondary amines at high pH	Reacts with thiol groups in cell Disrupts protein synthesis Affects enzyme activity
Chloromethyl isothiazolinone / Methyl	Broad spectrum bactericide	Denature > 60°C Inactivated by sulphydyl	Reacts with thiol groups in cell

isothiazolinone	Broad spectrum fungicide Compatible with all surfactants	and amine groups at pH >8.5	Disrupts protein synthesis Affect enzyme activity
Diazolidinyl urea	Broad spectrum of activity	Formaldehyde donor Weak against fungi Reacts with sulphite	Alkylation of amine and sulphydyl groups of proteins and nucleic acid bases
DMDM Hydantoin	Broad spectrum of activity Effective over wide pH range (3.5 – 10)	Releases formaldehyde Some weakness in fungicidal activity Reacts with avobenzone	Alkylation of amine and sulphydyl groups of proteins and nucleic acid bases
Imidazolidinyl urea	Good bactericide	Formaldehyde donor Weak against fungi and Gram positives Reacts with Proteins	Alkylation of amine and sulphydyl groups of proteins and nucleic acid bases
Iodopropynyl Butylcarbamate (IPBC)	Good cost effective fungicide	No bactericidal activity Heat labile (>40°C) Ineffective with anionic surfactants	Inhibits nuclear division Release of iodine may also bind proteins
Methyldibromo glutaronitrile (MDGN)	Broad spectrum bactericide	Only suitable for rinse off formulations in EU	Reacts with thiol groups in cell Disrupts protein synthesis Affect enzyme activity
Paraben esters	Global approvals Reasonably heat stable	Limited water solubility Incompatible with non-ionics and some proteins	Protein denaturation May interfere with active transport across cell membrane
Phenoxyethanol	Good against Gram negative bacteria Global approval	High levels required Low water solubility (2-3%)	Membrane disruptor Inhibition of TCA cycle enzymes

It can readily be seen that any one of these materials is unlikely to provide the protection required, even if it is fully compatible with the formulation. Leave on preservation is where most problems occur. The formulations are typically more complex and thus more prone to inactivation of the preservative. Micelle formation can easily render the preservative bio-unavailable to contaminants and many of the more effective actives are disallowed for leave-on use, as can be seen in the table. Because of this many suppliers have patented the use of particular mixtures to provide broad-spectrum protection and a synergistic effect is also frequently claimed.

The Collaborative Group, USP 6,447,793, ,claims a composition that relies on the solvent properties of phenoxyethanol to solvate a number of other preservative actives to provide improved solubility and broad spectrum protection. Mixtures of phenoxyethanol (56%), glycerine or propylene glycol (15%), benzoic or sorbic acid (6%), chlorphenesin (16%) and methylparaben (7%) are claimed. The mixtures are said to be effective in killing a broad spectrum of microorganisms and consist of materials having world-wide approval, low toxicity and are compatible with a wide range of cosmetic ingredients, including nonionic, cationic and anionic surfactant systems.

McIntyre, USP 5,965,59 , claims a mixture of phenoxyethanol, DMDMH and IPBC is particularly suitable for the preservation of shampoos and other surfactant-based products. The Phenoxyethanol acts as a solvent for the DMDMH and IPBC. It is claimed that the liquid antimicrobial solution can be mixed with an aqueous medium, to achieve, at a relatively low dilution concentration, high levels of broad spectrum antimicrobial and antifungal activity and that such solutions are substantially water dispersible.

MGS Micropure supplies a number of blends. Paratexin DPE is a mixture of phenoxyethanol and methyldibromo glutaronitrile, which combine the advantage of broad-spectrum antimicrobial protection and the ease of liquid handling. It is effective at 0.1 – 0.3% in many formulation types, and is compatible with proteins and anionic, cationic and nonionic emulsifiers. It is formaldehyde-free and retains its activity over the range pH 4.0 – 8.0. It is not permitted for leave-on products. Suitable alternatives are Paratexin DPM and DPM2; each is a mixture of propylene glycol, diazolidinyl urea, methylparaben and propylparaben. They are accepted in the USA and EU for leave-on products, are liquid, are compatible with proteins and anionic, cationic and non-ionic emulsifiers and retain their activity over the range pH 3.0 – 7.0.

Paratexin LIN is a synergistic blend of methyldibromo glutaronitrile, Bronopol, phenoxyethanol, butylparaben and isobutylparaben giving the advantage of broad-spectrum antimicrobial protection and ease of liquid handling. Use concentrations are typically between 0.03 – 0.15% and such low use levels enhance the safety profile of the product. The low level of Bronopol has critical implications for nitrosamine formation in products containing amines. Evidence suggests that nitrosamine formation is not detectable in formulations containing both Paratexin LIN and amines such as triethanolamine and stearamidopropyl dimethylamine, even after prolonged storage. It is effective over the range pH 3.0 – 7.5 and is non-irritating to eyes, skin and mucous membranes at the recommended use concentrations. Many other blends are also available from MGS Micropure and from other suppliers.

ISP is well known for its Germall, Germaben and Suttocide preservatives and it launched OptiPhen, a mixture of phenoxyethanol in caprylyl glycol at In-Cosmetics 2004. Germall 115 is imidazolidinyl urea .The other Germall and Germaben compositions are mixtures incorporating diazolidinyl urea with a variety of actives. Suttocide A is sodium hydroxymethylglycinate. It is .stable and active up to pH 12 and can also be used in acidic conditions as low as 3.5, giving the formulator very broad pH flexibility as well as being able to adequately preserve alkaline products. It is permitted for all applications in the EU.

It is widely known that certain materials can improve preservative action. Propylene glycol and other diols have fungicidal and antimicrobial properties and also improve solubility of parabens. The chelating agent EDTA and its salts bind calcium and magnesium ions thus denying their availability to the microbial cell membrane. It is particularly useful against pseudomonades and Patent USP 5,550,145. Ferulic acid, a natural chelating agent extracted from rice bran, is also said to be effective. Bioglan AB, claims the use of lauric or myristic monoglyceride improves the preservative potential of antimicrobials. Dr. Straetmans supplies a number of glyceryl esters under the Dermosoft trade name which have antimicrobial activity against Gram +ve organisms when used at 2% or above. When used as additives for skin care products for their moisturising and skin feel properties they may make it possible to significantly reduce the normal preservative content. Inolex supplies glyceryl caprylate, capryl glycol, phenylpropanol, sodium levulinate and anisic acid, either as individual materials or in mixtures, as its range of Lexgard Bio-active excipients. Whilst recommended for their multifunctional attributes as moisturisers, co-emulsifiers and wetting agents they coincidentally have an effect against bacteria, moulds and yeast. Glyceryl caprate and glyceryl caprylate may be found in propriety brands of deodorants which are otherwise free of conventional bactericides.

Sorbic acid and its salts are a popular choice when formulators must avoid parabens and the other more usual preservatives. The activity of sorbic acid is effective, against yeasts and moulds, and to a somewhat lesser extent against bacteria. The activity of sorbic acid depends on the non-dissociated content and therefore on the pH of the composition, which is ideally 4.76, but it remains effective between pH4 – 6. A problem that may arise is brown discolouration caused by the sorbic acid. USP 6,592,880, Aktiengesellschaft, describes a method of inhibiting this discolouration by the addition of citric acid and its salts with allantoin. The citrate should be added at an additive to sorbate ratio of 1:1 and the allantoin from 1:2 to 1.

Schulke & Mayr have also looked at the discolouration problem caused by sorbates and suggest the use of Euxyl K700, a mixture of phenoxyethanol, potassium sorbate and tocopherol. An alternative is Euxyl K702, which is a mixture of dehydroacetic acid with phenoxyethanol and benzoic acid. Other parabens-free preservatives from Schulke &Mayr include Euxyl K500; a mixture of diazolidinyl urea, potassium sorbate and sodium benzoate, and Euxyl K600, a mixture of IPBC with polyaminopropyl biguanide and formic acid. It also produces various mixtures of the isothiazinones.

With the continued search for products that the consumer may perceive as being “safer” there is great interest in using so-called natural preservatives or even claiming that a product is preservative-free. A product may be preservative-free if it is completely free of water as this is a fundamental requirement for any microorganism likely to contaminate cosmetic products. If water is present then it may be denied to the microorganism by combining it with other ingredients, such as polyols, sugars, protein hydrolysates and amino acids. Reducing a product’s potential for supporting microbial growth is termed hurdle technology. Limiting water availability is one of the most effective hurdles although it has limited effect against yeast and moulds. However propylene glycol, butylene glycol and methyl propanediol are effective against yeasts and moulds and the author cannot understand why many suppliers of botanical extracts, which often contain in excess of 40% glycol, still insist on adding numerous other preservatives to their compositions. Reducing a product pH to less than 5.0 is also effective against most bacteria but not against yeast and moulds.

The desire to use natural preservatives creates the biggest problem for the formulator. No preservative may be used which does not appear in Annex VI Part 1 or 2 of the EEC Cosmetic Directive 76/768/EEC - including 7th. amending Commission Directive 94/32/EC. However, there is no legislation for those natural materials, which, when used for their beneficial effect on the skin, may coincidentally have a positive effect on the total preservative requirement of the formulation. Tony Dweck, www.dweckdata.com, is the acknowledged expert on the use of natural materials for cosmetics and has published extensively on the subject. Dweck suggests the use of citrus seed extracts, lichen (*Usnea barbata*), Japanese Honeysuckle (*Lonicera japonica*), Formosan Hinoki (*Chamaecyparis*) and other materials, which may be added to cosmetic products for other reasons but which coincidently have a preservative action.