

Assessing parabens, formaldehyde and MIT

The choice and application of effective preservation technology is an essential part of R&D work during the development of cosmetics. It is not only a disaster for the image of a brand if the finished product is found to be contaminated on the market. Much more, it is a potential risk for the consumer and legislation therefore demands a safe preservation and thorough microbiological testing of finished products. However, the image of preservation, or more precisely of certain preservatives, by the consumer is normally negative. There is little controversy among experts that efficient preservation is essential for the safety of cosmetics. But, naturally, as there are many choices of preservatives, there are different opinions about what can be considered the best of so many choices.

Many different topics may have to be considered for choosing the right preservative. First of all it is the demand of safe and efficient elimination of microorganisms. This seems obvious, but not every preservation system works in every formulation. There are essential mistakes made in formulating by using preservatives that may work in one formulation, but are inhibited by certain ingredients and ineffective in others.

A second issue is the use of a widely accepted and validated methodology for microbiological testing. A number of suppliers of preservatives offer

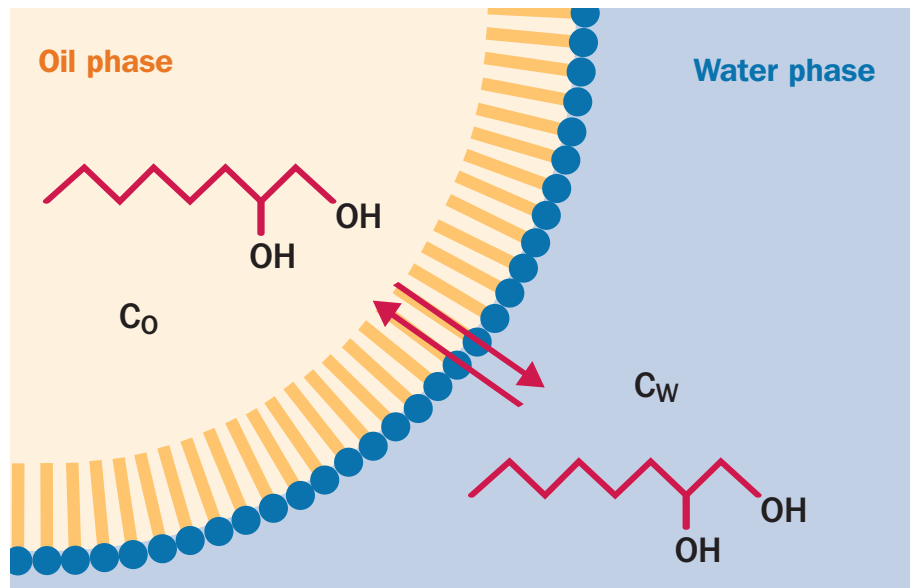


Figure 1: Distribution of antimicrobial active between water and oil phase. Ideally the solubility in water should be better compared to the oil solubility.

microbiological services (challenge testing) that are different to the methodology recommended by experts and authorities around the world (i.e. the challenge test according to USP, BP, Ph. Eur. ISO 11930 etc.). The mentioned validated methods used throughout the world all have in common that the same test organisms are used under comparable testing environments. In contrast to this, some preservative suppliers believe (or want to

make customers believe) that a testing for safe preservation needs a cocktail of germs and repeated inoculation of the test sample. This methodology has weaknesses (e.g. repeatedly diluting the product's preservation), low reproducibility and may lead to an excessive dosage of preservatives. An unnecessary high dosage of preservatives should be avoided for many reasons. It leads to higher formulation costs, but more important, is

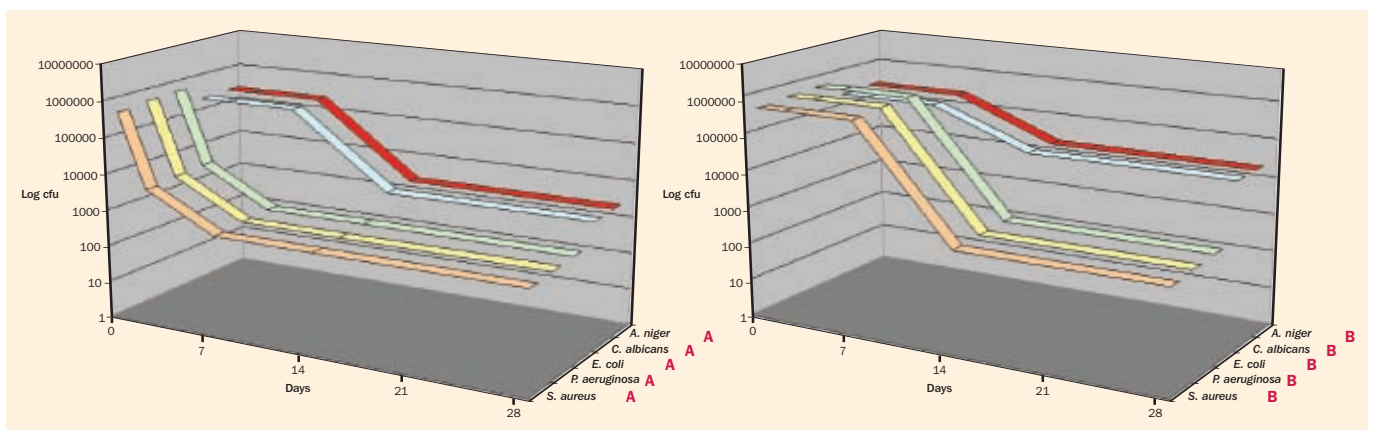


Figure 2: Logarithmical illustration of the required reduction of microorganisms to meet criteria A (left) and criteria B (right) of the test of sufficient preservation according to 'Efficacy of antimicrobial preservatives', European Pharmacopeia 5.1.3.

Table 1: Overview over the tested formulations.

Each formulation has been preserved either with 1% phenoxyethanol/parabens mix or 3% dermosoft® OMP

Entry	Formulation type	Basis	Oil Phase (INCI)	Additive/Active
1	Hydrogel	Acrylates/C10-30 Alkyl Acrylate Crosspolymer	–	PEG-40 Hydrogenated Castor Oil
2	O/W emulsion	Glyceryl Stearate Citrate	Ethylhexyl Stearate; Caprylic/Capric Triglyceride; Helianthus Annuus (Sunflower) Seed Oil	–
3	O/W emulsion	Glyceryl Stearate Citrate	Same as in entry 2	Kaolin
4	O/W emulsion	Glyceryl Stearate Citrate	Same as in entry 2	Water, Sea salt extract, Propanediol, Phospholipids, Stearoyl Inulin
5	O/W emulsion	Glyceryl Stearate Citrate	Same as in entry 2	Aloe Barbaden-sis Leaf Juice Powder
6	O/W emulsion	Cetearyl Glucoside, Cetearyl Alcohol	Same as in entry 2	–
7	O/W emulsion	PEG-100 Stearate; Glyceryl Stearate	Same as in entry 2	–
8	O/W emulsion	Hydrogenated Lecithin, C12-16 Alcohols, Palmitic Acid, Lecithin	Same as in entry 2	–
9	O/W sun lotion	Glyceryl Stearate Citrate	Butylene Glycol Dicaprylate/ Dicaprate Triheptanoic; Cyclopentasiloxane	UV-Filters
10	Hair Shampoo	SLES/ CAPB	–	–
11	W/O emulsion	Polyglyceryl-2 Sesquioleate, Polyglyceryl-3 Polyricinoleate	Mineral Oil, Isopropyl Palmitate; Caprylic/ Capric Triglyceride	–
12	W/O emulsion	Polyglyceryl-4 Diisostearate	Same as in entry 11	–
13	W/O emulsion	PEG-30 Dipolyhydroxystearate	Same as in entry 11	–

one of the reasons for an increasing number of adverse skin reactions to preservatives as stated by a number of studies in recent years. Thus, by recommending excessive dosage of preservatives, based on the shortcoming of their own microbiological methodologies, suppliers are helping to ruin the image of preservatives in general.

State of the art paraben replacement

It is surprising to see that every year hundreds of new cosmetic ingredients are introduced in the market, while the choice

of cosmetic preservatives remains more or less the same. On one hand a certain conservatism in this field is acceptable, because preservatives are well documented and risk assessment is calculable. On the other hand there is growing evidence about skin incompatibility with some (not all!) conventional preservatives. Serious studies around the world are showing this trend and published data about skin allergies, sensitisation and other adverse effects caused by preservatives is readily available. The data should be used carefully and wisely, certainly not to scare consumers. But this data must not be ignored either.

The past few decades have brought more light also on certain problems connected to the use of preservatives. More and more cosmetic manufacturers are moving away from many traditional preservatives. Some preservatives, like parabens, have been criticised for many years and replacement of these have led to a more frequent use of formaldehyde-releasers or isothiazolinones (CMI/MIT or other MIT mixtures). These ingredients obviously do not have a better dermatological profile compared to parabens, but, sadly, are often used to claim 'Paraben Free'. Some reactions in

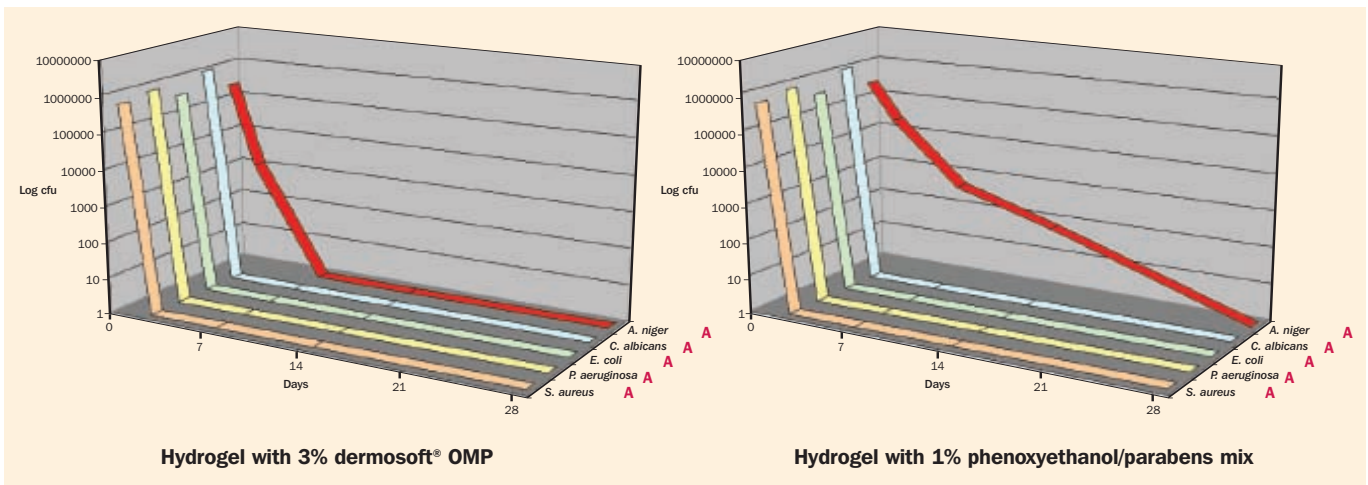


Figure 3: Hydrogel based on acrylates, no additive pH=5.5.

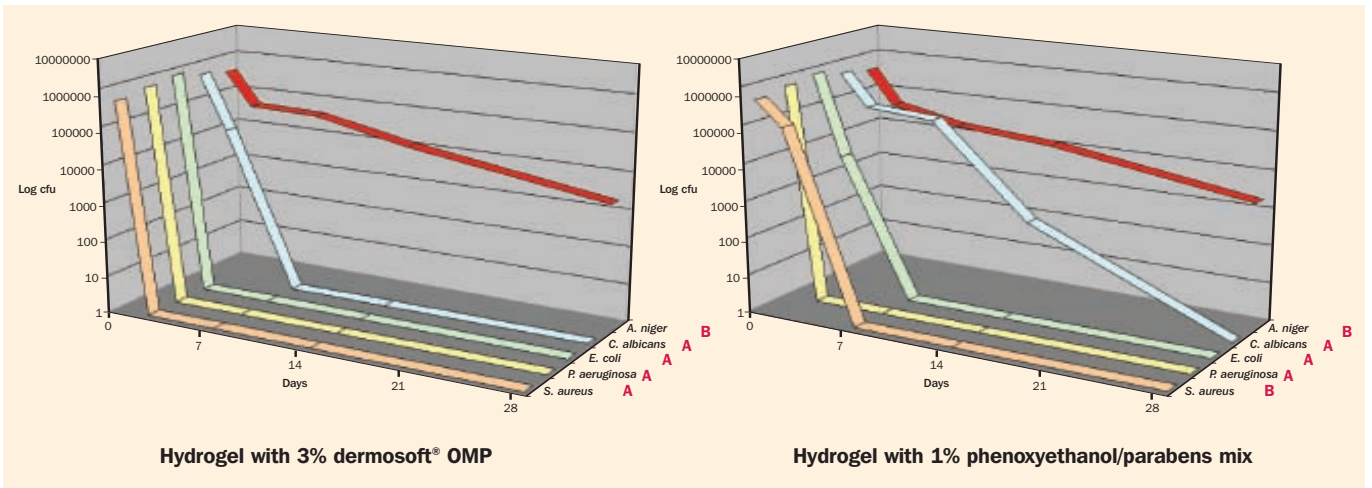


Figure 4: O/W-emulsion based on dermofeel® GSC, no additive pH=5.5.

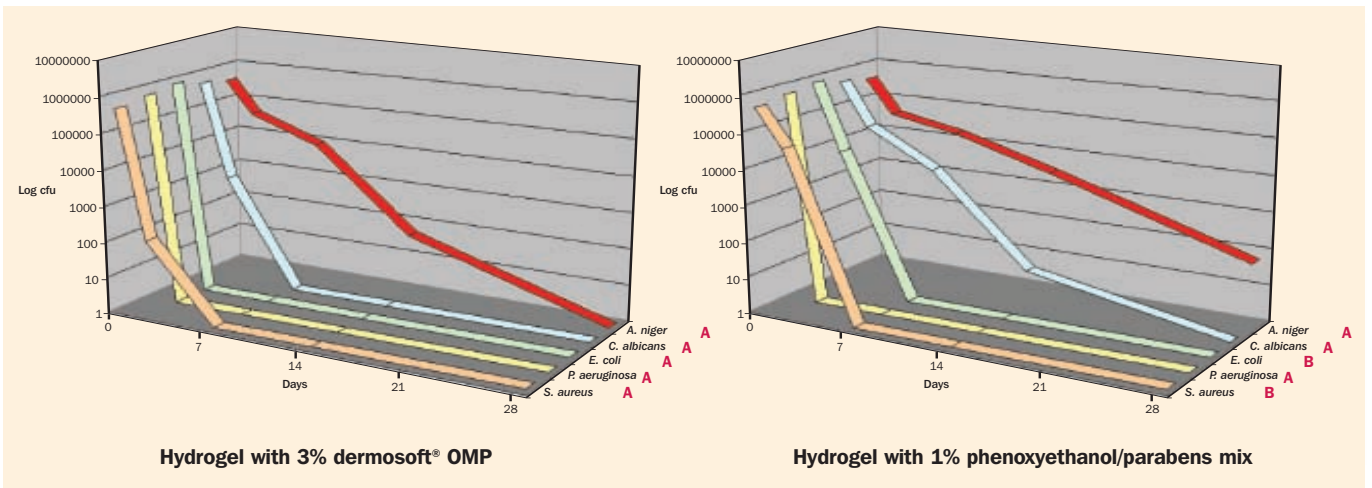


Figure 5: O/W-emulsion based on dermofeel® GSC, 7.0% Amazonian White Clay, pH=5.6.

the market (like the recent announcement of multinational companies to stop using formaldehyde-donors) have shown that this route may not be the right one to take.

And the winner is MIT

But it is worth remembering that the strongly increased use of methylisothiazolinone (MIT) based

preservatives not only has positive effects. The chemical group of isothiazolinones is known as a chemically reactive species which makes them very effective and economic preservatives at the lowest use levels. However, regarding the safety there has been evidence for many years that skin compatibility is poor. This resulted in the strict limitation of dosage of isothiazolinone

mixture (CMI/MIT) for use in leave-on products. Nevertheless, MIT on its own (combined with other preservatives) evolved into an attractive alternative for parabens in recent years. Ignoring the inherent chemical properties of the group of isothiazolinones the frequency of use grew constantly over the years and voices of concern by experts outside the industry

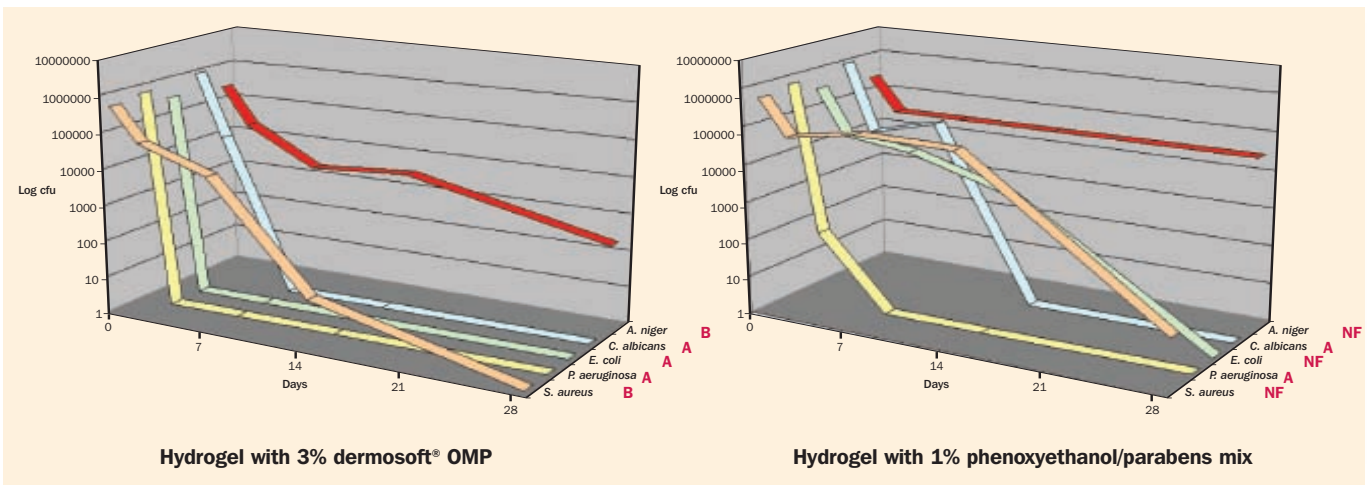


Figure 6: O/W-emulsion based on dermofeel® GSC, 3.0% Detoxium, pH=5.9.

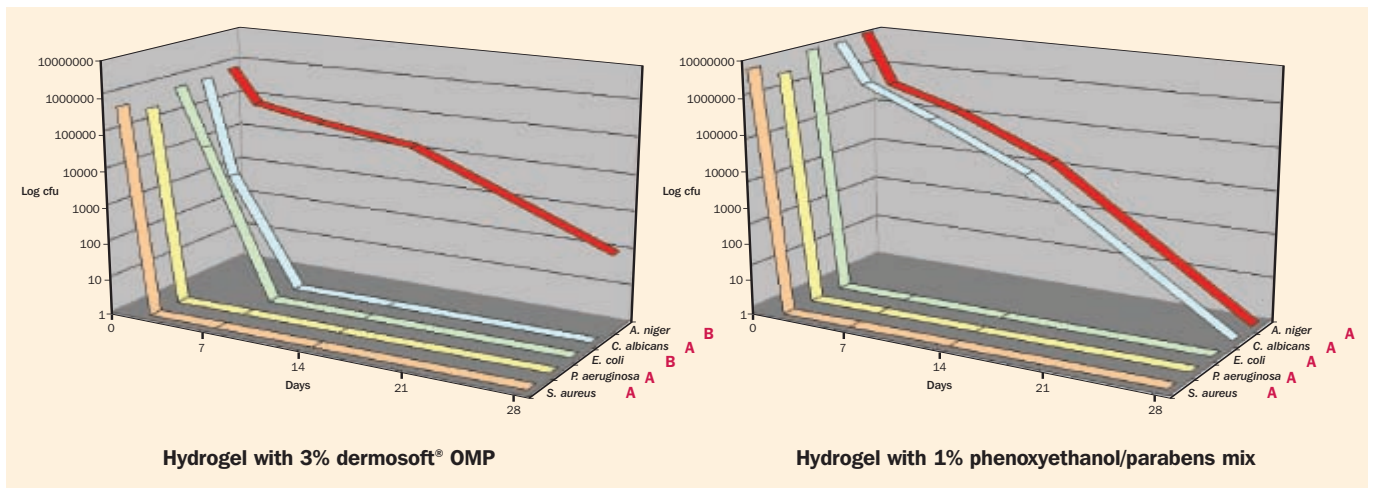


Figure 7: O/W-emulsion based on dermofeel® GSC, 2.0% aloe vera extract, pH=5.9.

have been getting louder. Dermatologists in different countries have pointed out that the limitation of MIT to a dosage of 100 ppm cannot be considered as safe and are suggesting significantly lower use levels. Studies in France, Germany, Denmark and Finland have come to similar conclusions, that MIT shows a frequency of allergy of approximately 1.5%. Also in the US concern is growing and has led to the dubious honour that the American Contact Dermatitis Society has awarded the title of 'Contact Allergen of the year 2013' to methylisothiazolinone.

The future trend for preservative use

There are many choices for preservation that can be considered effective and mild. A number of cationic surfactants (like benzalkonium chloride or polyaminopropyl biguanide, clorphenesin), aromatic alcohols (e.g. phenoxyethanol, benzyl alcohol) and organic acids (sorbic acid, dehydroacetic acid, benzoic acid and others) already present an effective tool box for preservation.

However, there are more antimicrobials that are legally not classified as preservatives, but have been used for many years in thousands of cosmetic products around the world. The concept behind these multifunctional ingredients was introduced approximately 30 years ago and is nowadays established in the cosmetic industry. The idea is to use cosmetic ingredients that have a multi-purpose use, e.g. as surfactants, wetting agents, pH-regulators or masking agents. At the same time they display strong antimicrobial properties even sometimes surpassing conventional preservatives in efficacy. This is used as a welcome secondary function in cosmetic formulations. The efficacy of preservation based on these ingredients has been demonstrated for decades in thousands of products on the market. It has to be mentioned that the same microbiological test methods are used to show the effectiveness of such systems in the same way as conventional preservation.

In this article a relatively new ingredient is discussed as a possible alternative for the above mentioned

conventional preservatives. dermosoft OMP is a blend of actives and efficacy enhancers that is tailored to address common problems in preservation. The cosmetic functions (wetting and masking) are complemented by excellent preservation quality. For 5 years this ingredient has been used in cosmetic products with no conventional preservatives necessary. A basic point in the concept of dermosoft OMP is the improvement of availability in the water phase. Every chemical substance has a natural distribution between water and oil. In dermosoft OMP (now referred to as 'the new multifunctional') this is altered with the help of a solvent in order to get a higher presence of the actives in the water phase. The result is a lower dosage of antimicrobials without the loss of efficacy.

In 2012 a study was conducted at Dr Straetmans to compare the efficacy of the new multifunctional with the typical parabens/phenoxyethanol blend still remaining the most widely used and trusted preservative system. Thirteen different cosmetic formulations were

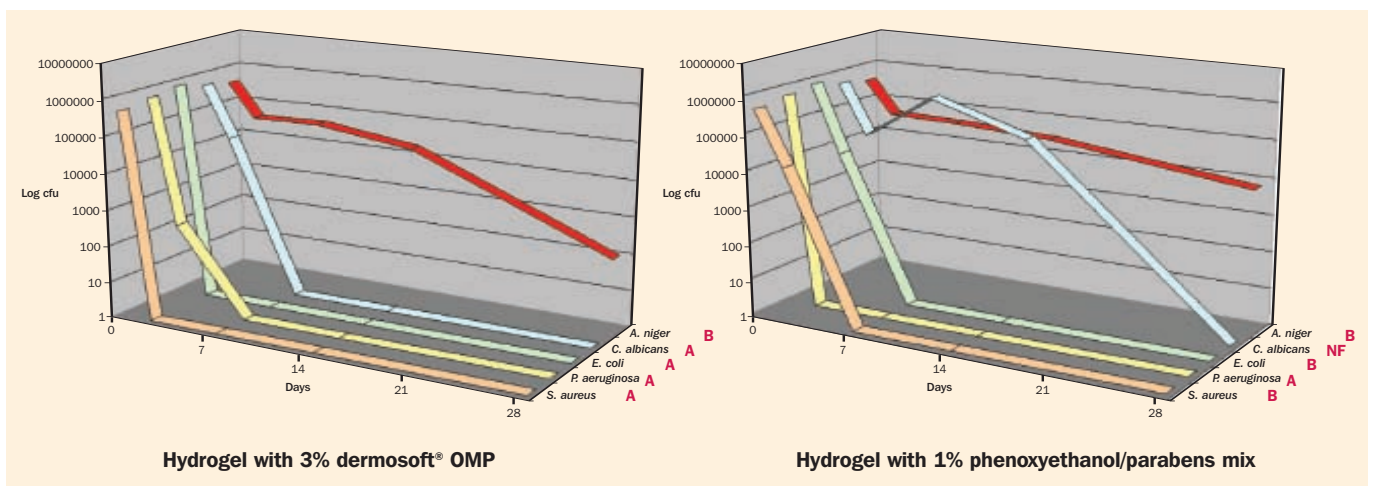


Figure 8: O/W-emulsion based on montanov 68, pH=5.5.

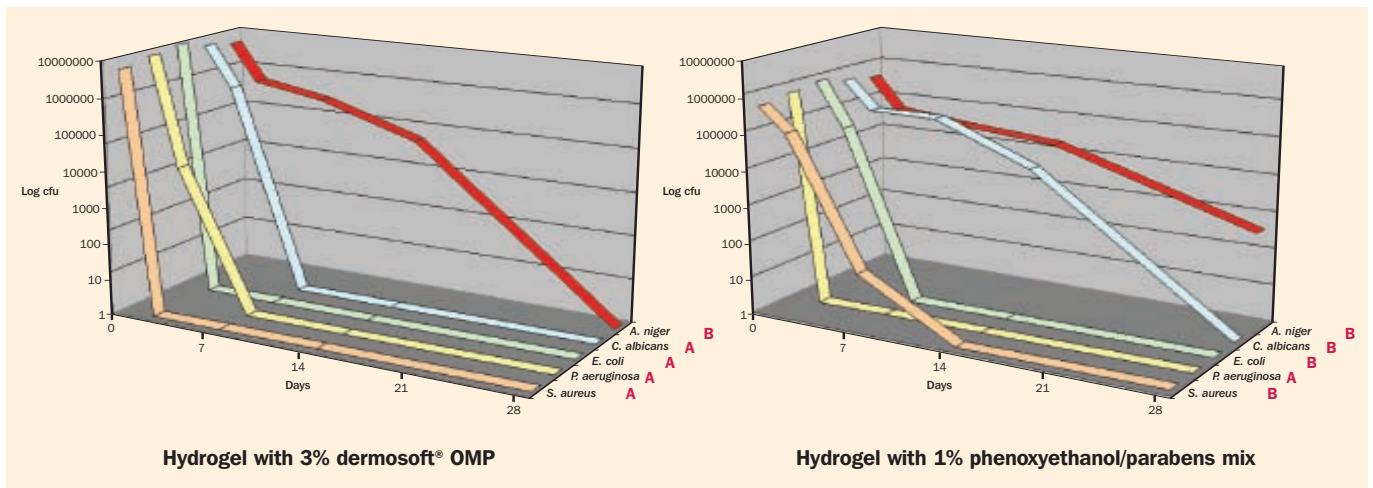


Figure 9: O/W-emulsion based on dracorin 100 SE P, pH=5.8.

selected to evaluate the preservation of both systems in a representative number of formulation concepts. Care was taken to choose basic formulations of different types (surfactant based, W/O, O/W, aqueous based), include different emulsifier types from various producers and also test formulations with potential inhibiting properties (e.g. sun care, high PEG loading, aloe vera or high mineral dosage).

The formulations were produced under identical conditions differing only in the type of antimicrobials used. A leading liquid phenoxyethanol/parabens mix was used with 1% dosage (1% active material in the finished product) and in the comparative formulations 3% the new multifunctional (0.5 active material in finished product) was used. All samples were tested in an independent accredited microbiological lab using the procedure described in chapter

5.1.3. of the European Pharmacopeia 2011. For that purpose, sterile samples of the formulations were separately inoculated with the following germs:

- *Staphylococcus aureus* (ATCC 6538), a Gram positive bacteria.
- *Pseudomonas aeruginosa* (ATCC 9027), as a Gram negative bacteria.
- *Escherichia coli* (ATCC 8739) as a Gram negative enterobacteria.
- *Candida albicans* (ATCC 10231) a representative of a yeast.
- *Aspergillus brasiliensis* (ATCC 16404) as a representative of a mould.

If the above criteria were not reached for one or more test organisms, the sample was judged as insufficiently preserved. Besides the antimicrobial stability the physical aspect and stability of all tested formulations was evaluated.

Results

Entry 1: Hydrogel based on acrylates

Due to the absence of an oil phase the preservation of a hydrogel is usually not a big challenge. This was confirmed in the challenge tests with both systems, the phenoxyethanol/parabens mix and the new multifunctional.

Impact of other ingredients on the preservation efficacy

Entry 2-8: O/W emulsions

The vast majority of cosmetic skin care products are oil in water emulsions. Due to the presence of two phases of different polarity, hydrophilic and lipophilic actives can be incorporated into the composition and the preserving system will be distributed between the two phases according to its specific solubility in them.

As described above, migration of the



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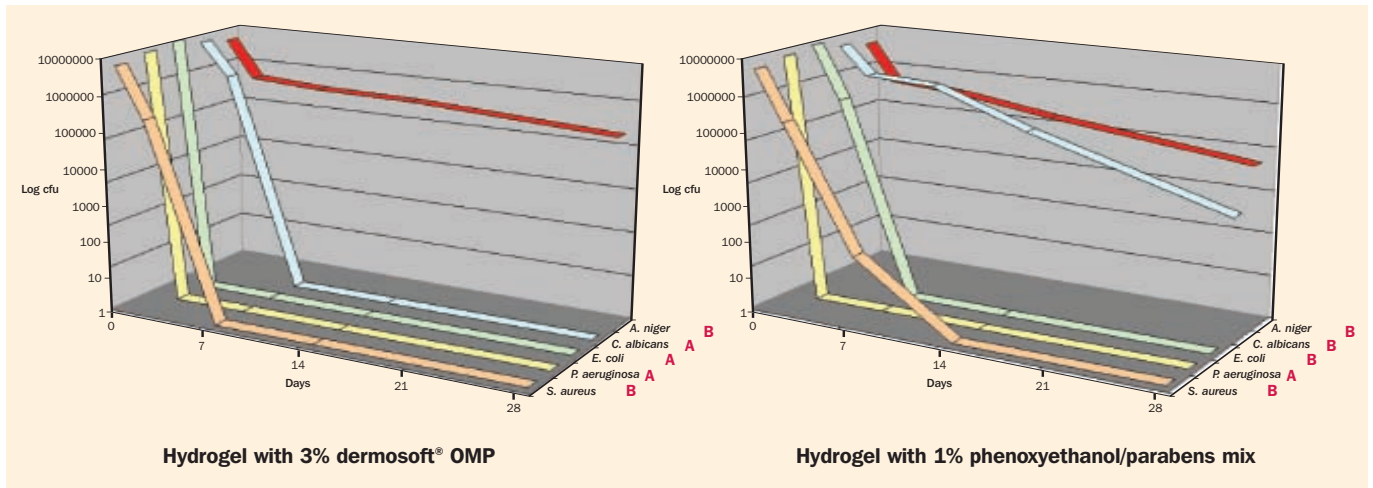


Figure 10: O/W-emulsion based on biophilic h/emulmetik 300, pH=5.7.

preserving system from the aqueous into the oil phase can lead to a more or less pronounced depletion of the antimicrobial active in the aqueous phase. Further, additives and actives can interact with the preserving molecules and thereby have a positive or negative impact on the efficacy of the preserving system used in the formulation.

As shown in Table 1 four O/W emulsions based on the same identical stabilising framework dermofeel GSC and identical oil phases were prepared. These emulsions contained different actives in the following quantities:

- **Entry 2:** No additive.
- **Entry 3:** 7.0% Amazone white clay (INCI: Kaolin) as a solid filler with potential adsorption capacity for the preserving actives.
- **Entry 4:** 3.0% Detoxium (INCI: Water, Sea Salt Extract, Propanediol, Phospholipids, Stearoyl Inulin) as a liposome containing active with potential trapping capacity for the preserving actives.
- **Entry 5:** 2.0% Aloe vera extract (INCI: Aloe Barbadensis Leaf Juice Powder)

as commonly used skin active and polysaccharide which can potentially interact with polar groups of preserving molecules.

The results of the challenge tests showed that the new multifunctional exhibited reliable antimicrobial efficacy in all tested systems while the phenoxyethanol/parabens mix failed to pass the test in the formulation containing liposomes (Entry 4b). Kaolin and aloe vera did not cause a significant difference between the two systems.

Influence of different emulsifiers

In order to investigate the effect of different emulsifying systems, three O/W-emulsions based on emulsifying systems other than glyceryl stearate citrate (Entry 2) but identical oil phases were tested.

- **Entry 2:** Dermofeel GSC (INCI: Glyceryl Stearate Citrate) as anionic emulsifier (tested above).
- **Entry 6:** Montanov 68 (INCI: Cetearyl Glucosides; Cetearyl Alcohol) as non-ionic sugar based emulsifier.

- **Entry 7:** Dracorin 100 SE P (INCI: PEG-100 Stearate, Glyceryl Stearate) as non-ionic polyethoxylated emulsifier.
- **Entry 8:** Biophilic H/Emulmetik 300 (INCI: Hydrogenated Lecithin, C12-16 Alcohols, Palmitic Acid, Lecithin) a phospholipid based lamellar emulsifier.

Comparing the efficacy of the tested preserving systems in emulsions based on different emulsifiers revealed that the new multifunctional again did not fail in any of the tested systems while the phenoxyethanol/parabens mix failed to comply with the demands of sufficient preservation against *Candida albicans* in the emulsion based on Montanov (Entry 6b).

Overall, in all cases the elimination of *Aspergillus niger* was the biggest challenge and finished in all tested systems only with B-criteria. Specifically against *Candida albicans* the new multifunctional provided a significantly better efficacy (all A-criteria) than the paraben blend of the phenoxyethanol/parabens mix (also B-criteria and failure).

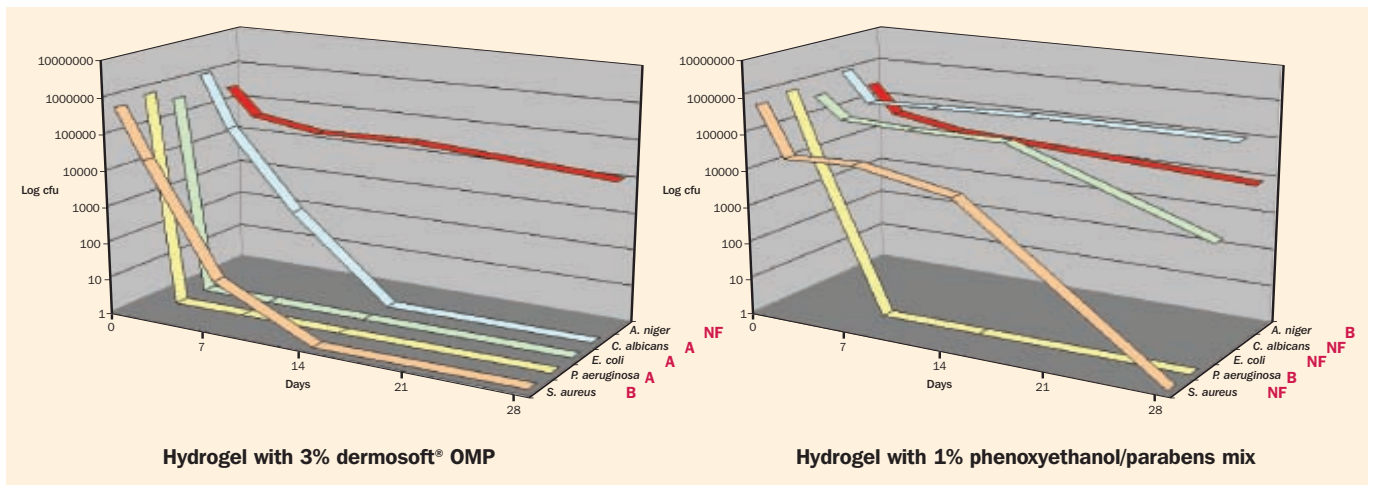


Figure 11: O/W-sun care lotion, pH=5.8.

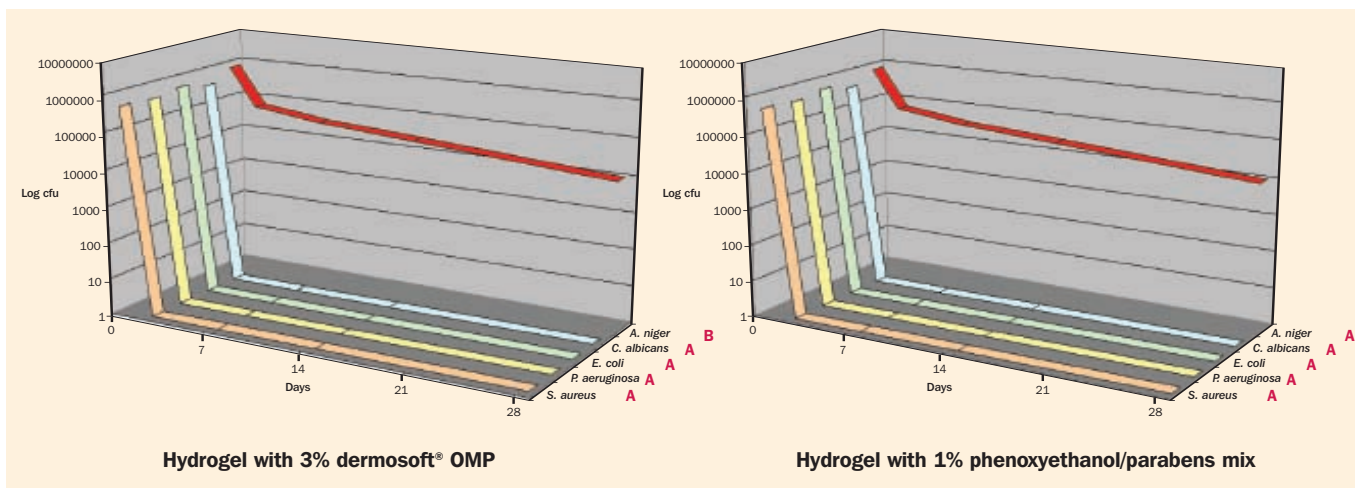


Figure 12: Hair Shampoo based on sodium laureth sulfate and cocoamidopropyl betaine pH=5.8.

O/W sun care formulation

One of the biggest challenges for a preserving system is the stabilisation of sun care products. Such formulations require high concentrations of polar oil phases. As described above, this can lead to a significant depletion of preserving system in the aqueous phase.

The formulation chosen to compare the efficacy of both test systems contained a polar oil phase based on butylene glycol dicaprylate/dicaprate and triheptanoin, the three chemical UV filters diethylamino hydroxybenzoyl hexyl benzoate, ethylhexyl methoxycinnamate and ethylhexyl triazone and silica coated titanium dioxide as physical UV filter.

The difference in the results of both challenge tests was significant. While the phenoxyethanol/parabens mix failed against a variety of bacteria and yeasts, the new multifunctional eliminated bacteria and yeast reliably. Both systems showed comparable efficacy against moulds. It is likely that the missing efficacy of the new multifunctional against moulds could be compensated by a slightly higher concentration.

Shampoo

Although neither parabens nor multifunctional systems based on surface active molecules like caprylyl glycol are the systems of choice for surfactant based formulations, it was decided to also include a surfactant based system into the present study. For that purpose a hair shampoo based on two standard surfactants, sodium laureth sulfate and cocoamidopropyl betaine was used for the comparative testing.

The results showed that both systems at the given pH worked reliably, with the new multifunctional being slightly more active against yeasts and the phenoxyethanol/parabens mix being slightly more active against moulds.

W/O emulsions

Finally, the effect of different emulsifying systems in water in oil emulsions was investigated. Three different W/O emulsions based on the following typical emulsifying systems and identical oil phases were compared with each other:

- **Entry 11:** dermofeel GO soft / dermofeel PR (INCI: Polyglyceryl-2 Sesquioleate, Polyglyceryl-3 Polyricinoleate)

- **Entry 12:** Isolan GPS (INCI: Polyglyceryl-4 Diisostearate, Polyhydroxystearate Sebacate)
- **Entry 13:** Citrol DPHS (INCI: PEG-30 Dipolyhydroxystearate)

In the tested systems the phenoxyethanol/parabens mix and the new multifunctional provided a reliable preservation with the new multifunctional being slightly more effective against bacteria and yeasts. For stability purposes the concentration of the new multifunctional was reduced to 2.5% in the formulations based on polyglyceryl-2 sesquioleate/polyglyceryl-3 polyricinoleate and polyglyceryl-4 diisostearate/polyhydroxystearate sebacate.

Conclusion

Thirteen formulations have been tested in order to investigate the efficacy of the new multifunctional in comparison to a standard blend based on mixed parabens and phenoxyethanol. The findings of the study are summarised in Table 2.

The results indicate a superior efficacy of the multifunctional blend dermosoft OMP

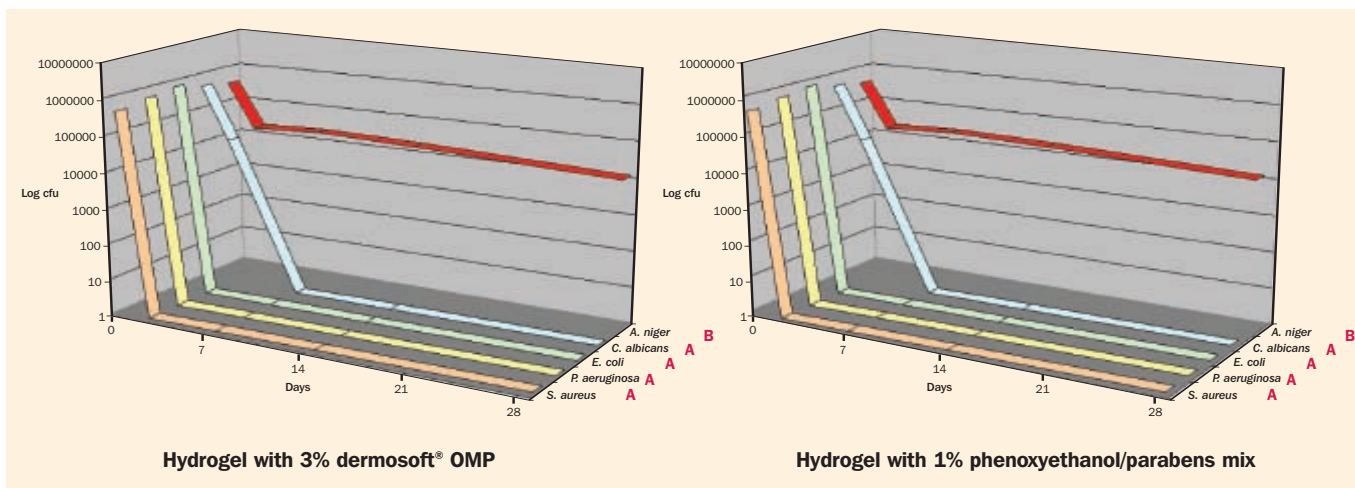


Figure 11: O/W-sun care lotion, pH=5.8.

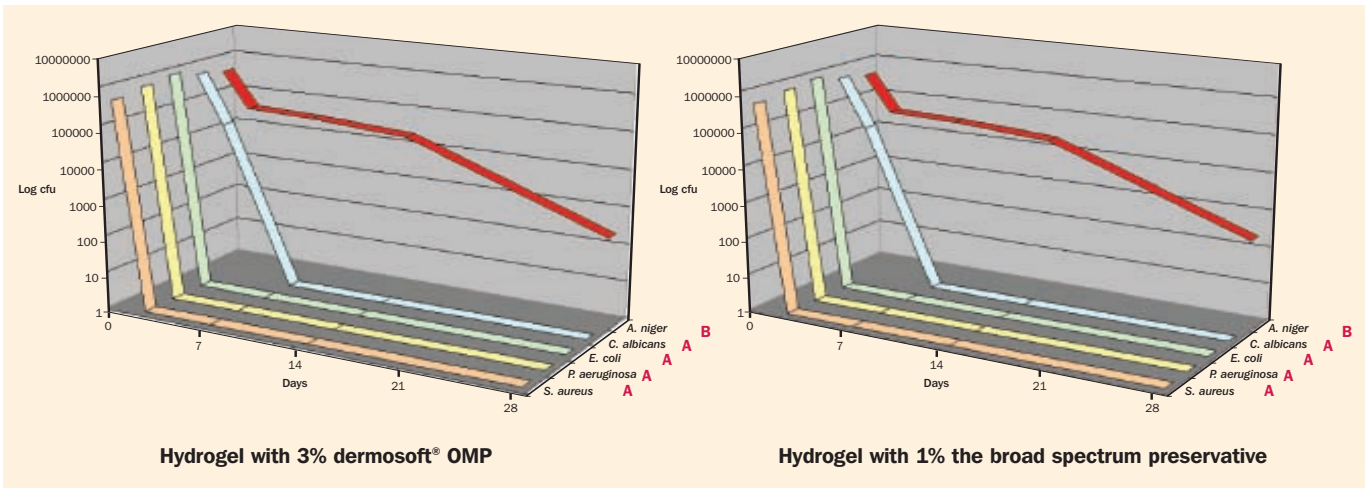


Figure 14: W/O-emulsion based on isolan GPS, pH=5.6.

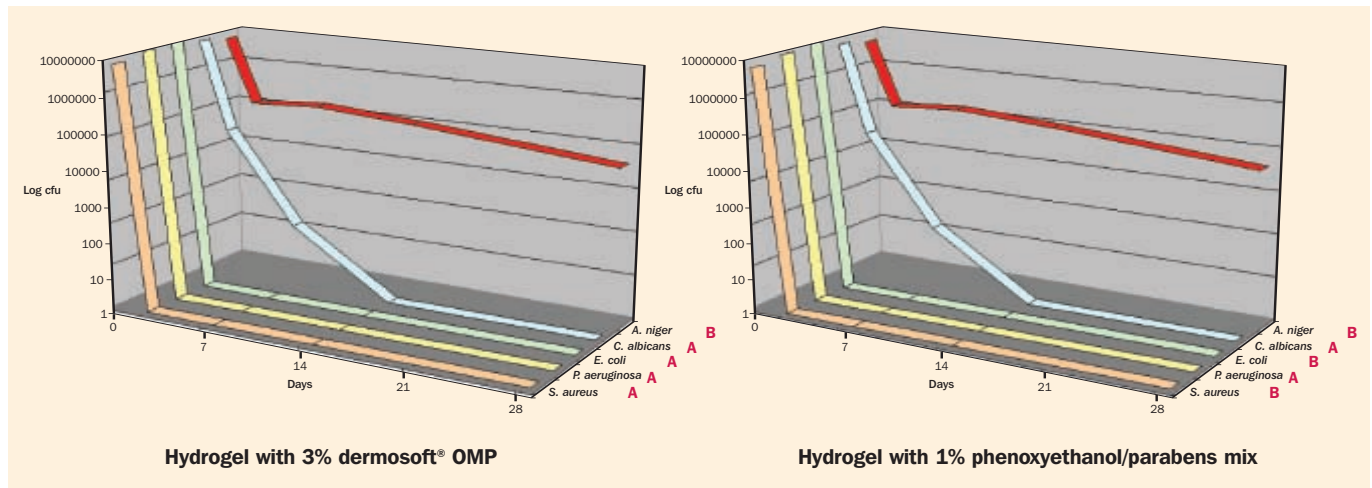


Figure 15: W/O-emulsion based on citrol DPHS, pH = 5.6.

against bacteria and yeast. While the parabens blend failed to provide a sufficient preservation capacity against bacteria and yeast in several cases, dermosoft OMP showed a very good antimicrobial action against these microorganisms and completed the challenge test mainly with A-criteria.

Against moulds the efficacy of dermosoft OMP and the phenoxyethanol/parabens mix was comparable.

In the stability testing almost no differences between identical formulations

preserved with 3.0% dermosoft OMP and 1.0% the phenoxyethanol/parabens mix were observed, only in two W/O emulsions a reduction of the concentration of dermosoft OMP to 2.5% was required. Comparing the physical aspects of the tested formulations revealed that the viscosity of the formulations preserved with dermosoft OMP in some cases was slightly lower than the one of formulations preserved with the phenoxyethanol/parabens mix.

The present study demonstrates that

dermosoft OMP in a broad variety of formulations can serve as a very good alternative to parabens blends. Even in the presence of different potential inhibitors dermosoft OMP proved to show a similar or even better antimicrobial efficacy. Being easy to incorporate into the tested formulations, stable over a broad pH range and showing to be compatible with a broad variety of cosmetic raw materials, dermosoft OMP therefore complied with all technical demands to a reasonable parabens alternative.

Due to the physical mode of action, adverse effects on the skin, are less likely to occur with dermosoft OMP than with chemically acting preservatives. Further, neither the extensively studied toxicological properties of the components forming dermosoft OMP nor the long history of their use did reveal any specific risks associated with a use in dermal application.

It therefore can be concluded that dermosoft OMP provides a reliable and safe alternative for all formulators who are challenged with the project to replace parabens or any other type of preservatives in cosmetic formulations.

Table 2: Summary and analysis of the challenge test results.

	3.0% dermosoft® OMP			1.0% phenoxyethanol parabens mix		
	A	B	Failed	A	B	Failed
<i>Staphylococcus aureus</i>	10	3	–	5	6	2
<i>Pseudomonas aeruginosa</i>	13	–	–	12	1	–
<i>Escherichia coli</i>	12	1	–	6	5	2
<i>Candida albicans</i>	13	–	–	9	2	2
<i>Aspergillus brasiliensis</i>	2	10	1	4	8	1
	50	14	1	36	22	7