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MicroSilver BG™

Silver microparticles
Purifying dermo-cosmetic care

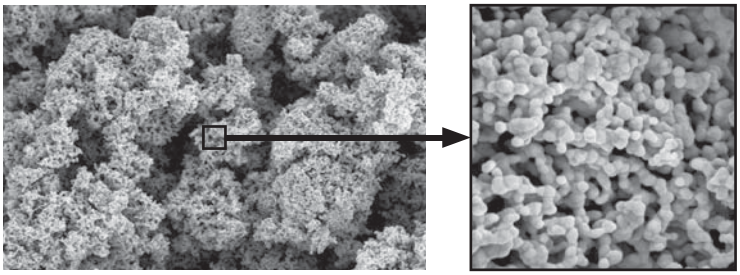
- Innovative and natural form of silver
- Pure metallic active substance
- Supports treatment and regeneration of problem skin thanks to its antimicrobial and anti-inflammatory effect
- Complies with the ECOCERT Natural and Organic Cosmetics standards

Table of Contents

What is MicroSilver BG™ ?

MicroSilver BG™ is an innovative form of pure metallic silver, the product of more than 15 years of research at the Fraunhofer Institute in Germany.

- Bio-Gate uses exclusively pure metallic silver for the production of MicroSilver BG™
- Only this unique and complex production process produces the special surface structure of MicroSilver BG™. It guarantees the release of silver ions over a longer time span (depot and time-release effect)

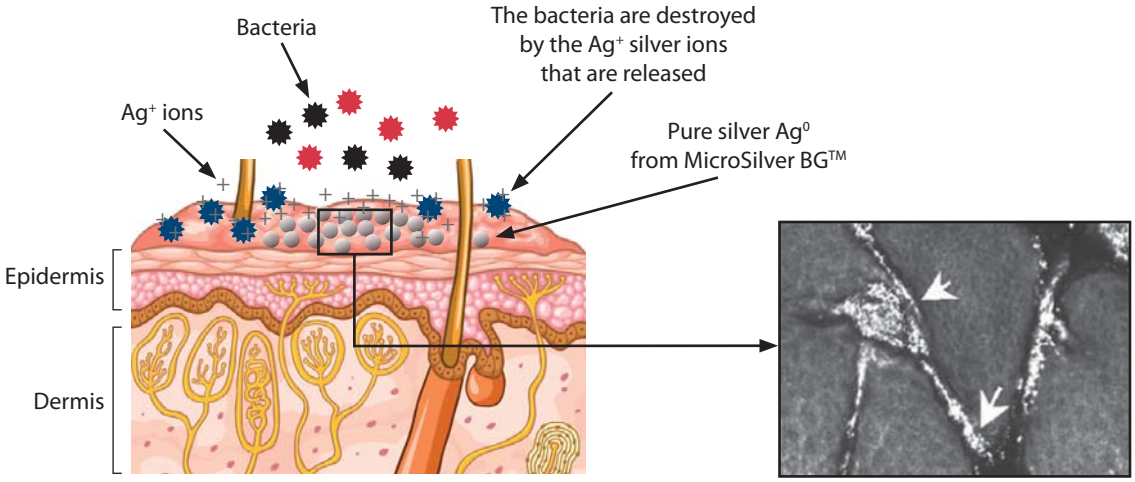


Structure of MicroSilver BG™: mean diameter of the particles: 10 µm

MicroSilver BG™ is manufactured in production facilities specially developed by Bio-Gate for this purpose. A purely physical gas phase process allows, thanks to the use of elemental silver of a high level of purity, production without any ionic form containing silver. This manufacturing technology is unique and is made available exclusively to BioEpiderm for cosmetic applications.

MicroSilver BG™ - How it acts on the skin

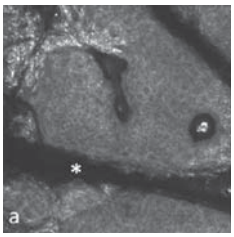
The germicidal action of silver comes from the formation of soluble silver ions. It is the effect of the inactivation of certain enzymes and the lesion of bacterial membranes through the silver ions that are released.



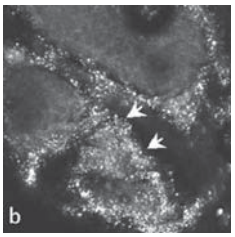
Confocal laser microscope: absorption of Ag at the surface of the keratinocytes. Accumulation of MicroSilver BG™ (white arrows) in the skin folds of the epidermis surface.

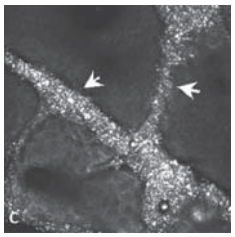
How MicroSilver BG™ acts on the surface of the skin

A study of the surface of the skin using confocal laser microscopy allowed a highlighting of the exclusively surface action of MicroSilver BG™ :

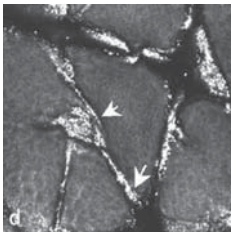


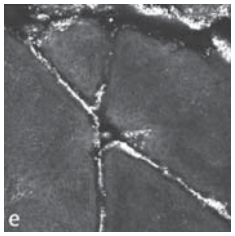
Healthy skin: keratinocytes and skin folds (*) in a normally aged skin.





Same area immediately following application of a cream containing 0.5 % MicroSilver BG™: the highly refractile silver particles are found both on the surface of the skin (b, arrow) and in the skin folds (c, arrow).





Two hours after the application:
the silver particles are found in the skin folds (d) and in the follicular openings (e). More detailed explanations in the text.

Two hours following application of a body milk containing 0.5 % MicroSilver BG™, the silver particles (see white arrows) are primarily observed in the skin folds. Identical results were obtained through a horizontal and vertical cartography. No particles of silver were identified in the epidermis and the upper layers of the dermis (a to d). (Photo: Ulrich)

Conclusion

➔ MicroSilver BG™ collects mainly at the pore level and in the skin folds.

➔ MicroSilver BG™ acts on the surface. The silver ions are released to the surface of the skin and may thus react with the surrounding bacteria and yeast/fungi (e.g. golden staphylococcus).

Dermo-cosmetic properties

MicroSilver BG™
- is active against a broad spectrum of bacteria
- supports treatment of irritated and inflamed skin
- is extremely effective, even at a low dosage
- has a long-lasting effect (depot and time-release effect)

Antimicrobial effect
MicroSilver BG™ forms an invisible protection at the surface of the skin, which quickly eliminates unwanted micro-organisms.

Regularizing and stabilizing effect on the skin microflora
In an optimal concentration, MicroSilver BG™ does not destroy the skin flora, but prevents the development of unwanted micro-organisms and, thanks to its anti-inflammatory effect (bibliographic information – scientific publications), it helps to re-establish the optimal physiological balance of the skin microflora.

Strengthening effect on the skin microflora
When used regularly, MicroSilver BG™ strengthens the resistance of the skin to any colonization of potentially disease-causing substances. Incidents of inflammation are lowered and controlled.

Areas of application
MicroSilver BG™ may be used any time purifying action is desired.

To prevent secondary infections
- Supports treatment of atopic skin
- Supports treatment of dry skin and damaged lips
- Post depilation and aftershave products

To prevent the formation of odours
- Deodorants
- Foot care

To fight against the responsible agent
- Supports treatment of skin with a tendency to form acne
- Supports treatment of imperfections: mature problem skin
- Anti-dandruff shampoos
- Toothpastes, mouthwashes

Products with a high concentration of MicroSilver BG™ are intended for
- Use in the case of skin irritations such as redness, zones of the skin with a high formation of moisture
- Support specific treatments (neurodermatitis, atopic dermatitis). Here, the silver ions act against Staphylococcus aureus

Finally, MicroSilver BG™ may allow the concentration to be decreased or even, in certain cases, the preservative agent in your cosmetic formulation to be eliminated (see page 10).

Conclusion

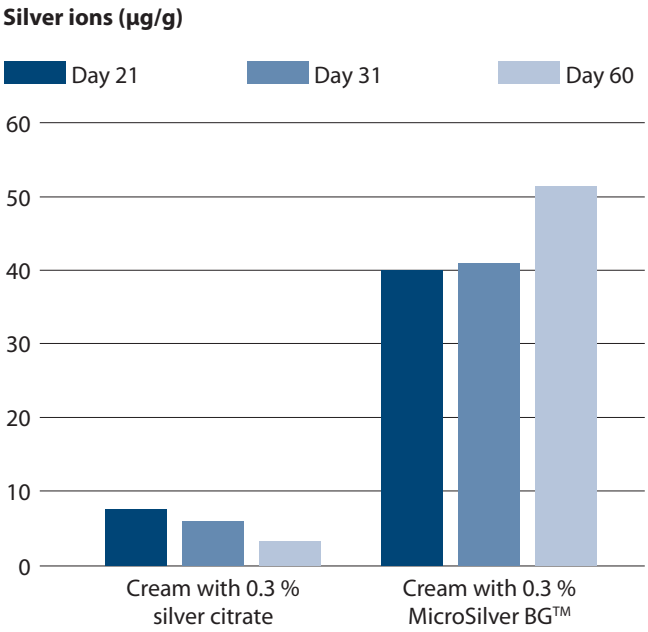
➔ **MicroSilver BG™ allows for an innovative approach and an advanced formulation for your new ranges of body care products.**

Why choose MicroSilver BG™ over other forms of silver?

Silver salts

As pure metallic elemental silver, MicroSilver BG™ must be distinguished from silver salts (citrate, for example).

- MicroSilver BG™ does not darken the colour of the finished product due to the fact that it does not contain silver salts.
- The colour of the cosmetic product does not change over time.
- The preservative content may be reduced thanks to the use of MicroSilver BG™.
- Long-lasting effect: in comparison with traditional silver powder, MicroSilver BG™ offers a far superior total free surface thanks to its sponge-like structure. MicroSilver BG™ is thus able to generate enough silver ions and over a long period of time (depot and time-release effect).
- A study has shown the superiority of MicroSilver BG™ in formulation (see below). Thanks to its composition and special structure, MicroSilver BG™ guarantees a level of silver ions in the finished product that is superior to that obtained with an identical concentration of silver in the form of salt. There is thus better antimicrobial efficacy over time.



Concentration of silver ions over time in a cream with 0 3 % silver citrate and 0.3 % de MicroSilver BG™

Colloidal silver

Colloidal silver, also called „silver water", has a mean particle size of around 50 nm. At the moment, however, the nanoparticles are not the subject of any reassessment. The mean size of MicroSilver BG™ particles is 10 µm. MicroSilver BG™ is therefore not concerned about any debate with respect to nanoparticles.

Technical information

INCI	Silver (CI 77820)
Appearance	Homogenous powder that is silver-gray in colour
Odour	Odourless
CAS Number	7440-22-4
REACH	Pre-registered
ECOCERT	Complies with the ECOCERT Natural and Organic Cosmetics standards
Preservative	None
Adjuvant/Additive	None
Nanoparticle	None
Boiling point	2210°C
Melting point	960°C
Density	Approx. 10.5 g/cm^3 (20°C)
Solubility	Indissoluble in water
Surface	Up to 5 m^2/gr
Average Ø of the particles	10 µm
Standard packaging	0.5 kg and 2 kg

➔ MicroSilver BG™ is composed of ultra-pure natural silver. It does not contain any additives or adjuvants, and has a long-lasting effect thanks to its sponge-like structure that provides it with a very sizeable total free surface (5 m^2/gr).

Recommended dosages

Optimal dosage ..... 0.1 %

Body/facial care.....0.1 % - 0.3 %

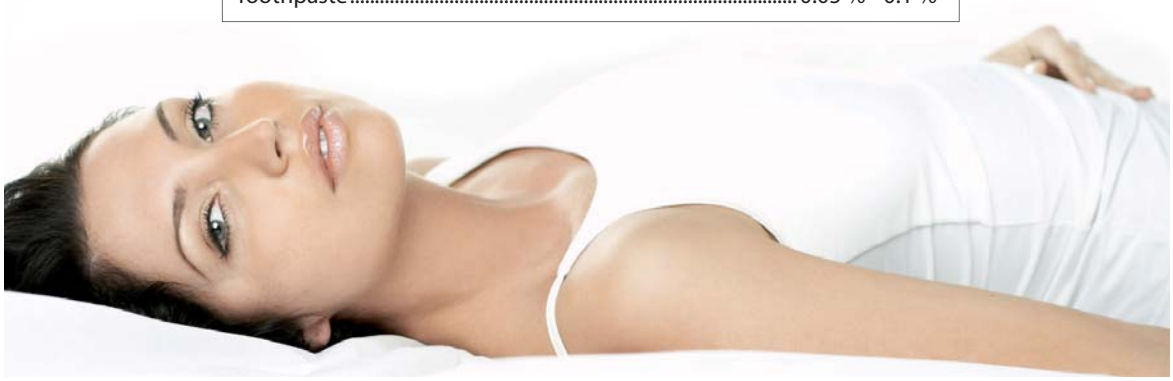
Shampoo.....0.1 % - 0.2 %

Foot care.....0 2 % - 0.4 %

Hand care.....0.2 %

Lip care.....0.05 % - 0.1 %

Toothpaste.....0.05 % - 0.1 %



Efficacy test: Dry skin with an atopic tendency

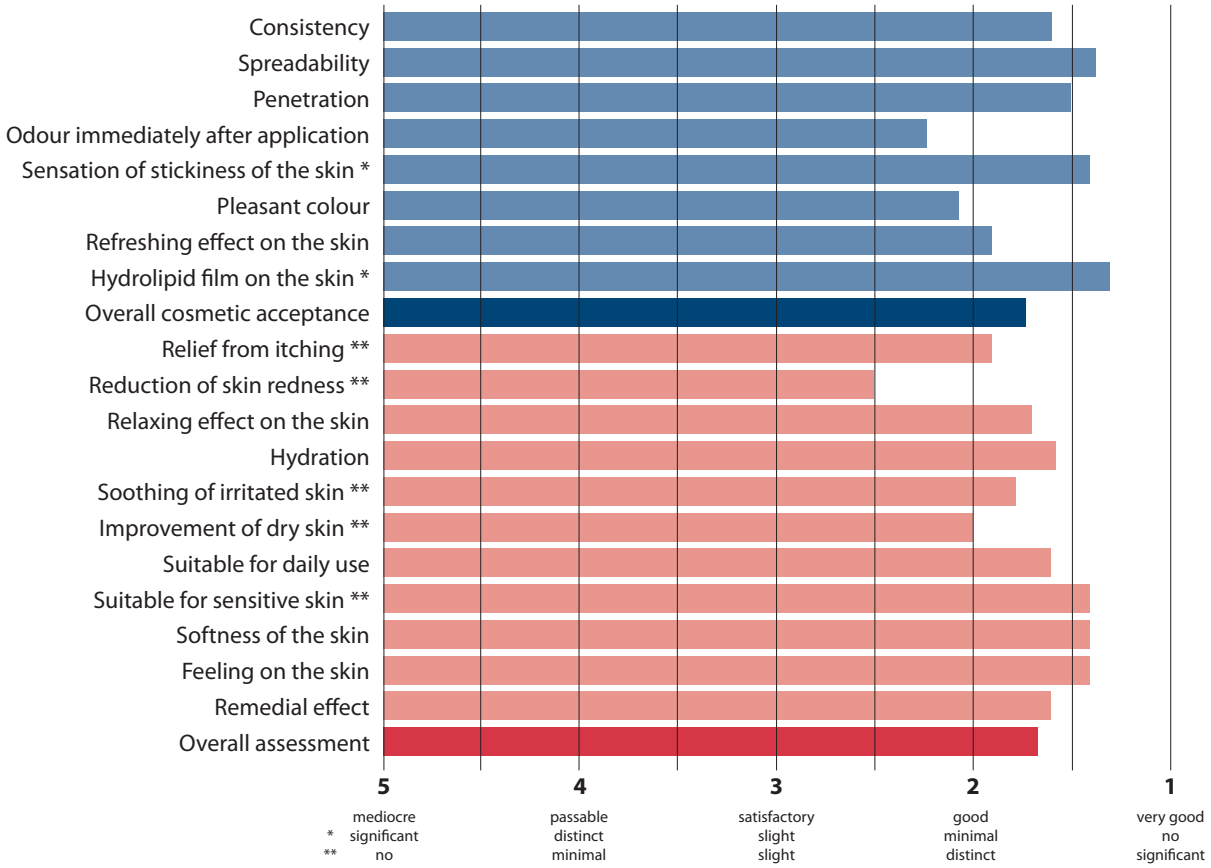
- Study conducted by the Schrader Institute, Holzminden (Germany)
- 30 volunteers having dry skin with an atopic tendency (1/3 of the subjects)
- Age: 18-64 years old, average age: 45
- 2 applications daily for 4 weeks
- During the study, the atopic subjects did not display any symptom (SCORAD under 15)
- Product tested: body milk containing 0.1 % MicroSilver BG™

Results obtained after 4 weeks of use of the milk

- Clear relief from itching
- Decrease (from slight to distinct) of skin redness
- Soothing of irritated skin
- Improvement of dry skin

Evaluation of body milk containing 0.1 % MicroSilver BG™

Mean values, n = 30 participants

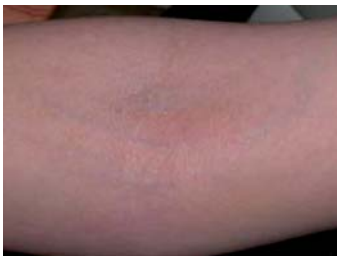


Efficacy test: Atopic skin

- Clinical study conducted by Vitaklinik, Kiel (Germany)
- 20 patients suffering from atopic eczema
- 2 applications daily for 4 weeks of a cream containing 0.1% of MicroSilver BG™
- Study of the change of local SCORAD (standard process used in dermatology. Assesses the severity of the symptoms of redness, oedema and formation of papules, oozing and crust formation, excoriation and skin thickening (lichenification)
- Study of the change of general SCORAD (assesses the propagation of the dermatosis and the degree of severity of the areas concerned as an objective parameter of the disease and the patient suffering as a subjective parameter of the disease)
- No other systemic or topical treatment was applied during the test

Before treatment

After 4 weeks of treatment with a MicroSilver BG™ level of 0.1 %



Average change of local SCORAD

Week 0	Week 2	Week 4
8.7	6.1	4.1

Examples

Patient no.	Week 0	Week 2	Week 4
3	11	2	
5	9	5	3
7	6	7	1
13	12	5	2

The start values were in a range of 2 to 15.
(Maximum possible score: 15)

Average change of general SCORAD

Week 0	Week 2	Week 4
51	36	25

Examples

Patient no.	Week 0	Week 2	Week 4
3	66	11	
5	43	25	18
7	38	36	7
13	48	33	11

The start values were in a range of 19 to 73.
(Maximum possible score: 103)

Results

- MicroSilver BG™ reduces the local SCORAD index in a statistically significant manner from 8.7 to 4.1. This means that the visible symptoms of the disease, such as redness, oozing, crust formation, are markedly less pronounced.
- MicroSilver BG™ reduces the general SCORAD index from 51 to 25: the patients have a better opinion of their general state.

Efficacy test: Oral hygiene, periodontitis

Clinical study intended to evaluate a toothpaste containing 0.05 % of MicroSilver BG™ on patients showing obvious periodontitis.

Principles of the study	Open monocentric clinical study
Objective of the study	Monitoring of the antimicrobial effect of toothpaste
Study centre	Dental Clinic 1 – Preservative Treatments and Periodontology, Erlangen University Dental Clinic (Germany)
Person in charge of the study	Professor Frankenberger
Product tested	Toothpaste containing 0.05 % of MicroSilver BG™, 1 % of zinc gluconate and 1 % of dexpanthenol
Sample group	25 patients

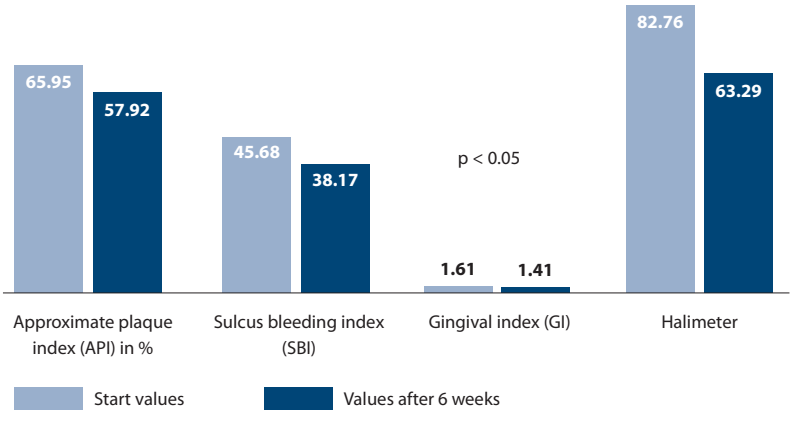
Target criteria
The purpose of the clinical study is to determine if, within the framework of dental oral hygiene at home, the toothpaste used with small interdental toothbrushes is able to reduce in any significant manner the germ markers of periodontitis and the signs of inflammation.

The following parameters are measured
- Approximate plaque index (API)
- Sulcus bleeding index (SBI)
- Gingival index (GI)
- Halimeter
- Biological germ markers

Study process
- Information and inclusion of the patients in the study
- Instructions with respect to oral hygiene. Determination of the start values
- Handing out the medication that is the subject of the study
- After 6 weeks, new check and new determination of the parameters

Outline of treatment
- Daily brushing of teeth in accordance with instructions given by the Clinic

Results
- Significant improvement of inflammation parameters ($p<0.05$)
- Significant reduction ($p<0.05$) of the microbiological germ markers (here, the germ responsible for the periodontitis is Aggregatibacter Actinomycetemcomitans)
- No secondary side effects were observed



➔ **MicroSilver BG™ reduces microbiological markers of periodontitis and the parameters of inflammation in a significant manner.**

Efficacy test: Microbiological protection of an emulsion

Sample	Absorbent cream containing 0.1 % MicroSilver BG™
INCI	AQUA, CAPRYLIC/CAPRIC TRIGLYCERIDE, GLYCERYL STEARATE, GLYCERIN, CETYL ALCOHOL, PANTHENOL, CETEARETH-30, TOCOPHEROL, CETEARETH-12, FRAGRANCE, SILVER, ZINC GLUCONATE
Testing method	In accordance with the European Pharmacopoeia 5.1.3, table 5.1 3-2 (topical preparations)

Germs tested	**2 days**	**7 days**	**14 days**	**28 days**
Staphylococcus aureus	★★★	★★★	★★★	★★★
Pseudomonas aeruginosa	★★★	★★★	★★★	★★★
Candida albicans	★★★	★★★	★★★	★★★
Aspergillus niger	★★★	★★★	★★★	★★★

★★★ : higher than the recommended efficacy level
★★ : corresponds to the recommended efficacy level
★ : lower than the recommended efficacy level but above the recommendations

➔ **The sample is in compliance with the specifications of the European Pharmacopoeia 5.1.3, table 5.1.3-2, criteria A, relative to the antimicrobial preservation of topical preparations. MicroSilver BG™ containing 0.1 % provides the product tested with satisfactory microbiological protection.**

Safety: Toxicology studies

In vitro test: Skin penetration using the Franz diffusion cell

A: Absorbent cream DAB, 1.5 % of MicroSilver BG™
B: Absorbent cream DAB, 0 5 % of MicroSilver BG™
C: Absorbent cream DAB, 0.5 % of MicroSilver BG™ + 3 % of dexpanthenol

☑ **No diffusion of MicroSilver BG™ through the membrane and only minimal penetration of the silver ions.**

Comparison of the data with the risk analysis based on the reference scientific values for skin penetration: the application of 2 g of a cosmetic cream on a skin surface of 10 cm x 10 cm (equivalent to a large quantity applied), corresponds to:

- Surface concentration ..... 20 mg/cm²
- Evaluation of risk potential ..... 0.2 – 10 ng* of silver
- Value measured ..... 1.5 – 4 ng** of silver

* Tested for a sample with 1 % of MicroSilver BG™ (or 10 times the recommended dosage)
** Measured on samples with 1.5 % and 0.5 % of MicroSilver BG™

☑ **A good correlation between the risk analysis data and the test data was observed.**
☑ **As expected, the skin penetration may be considered as being insignificant.**

Clinical test: Tape stripping test following application of an emulsion

Application of 2 mg/cm2 of a cream with 0.1 % and 0.5 % MicroSilver BG™ on the left or right forearm on 10 volunteer subjects for 28 days, with 2 applications daily (mornings and evenings).

Method — Before starting use (control) and after 28 days, 60 strippings (3M® adhesive tape) are carried out. This number corresponds to the elimination of all of the stratum corneum (SC).

Results — Quantity in % of the dosage of silver applied found in the SC (60 adhesive tapes) after 28 days:
- Cream MicroSilver BG™ 0.1 %: 0.064 % of silver
- Cream MicroSilver BG™ 0.5 %: 0.049 % of silver

☑ **These results correspond perfectly with the results of test on the Franz diffusion cell and confirm the insignificant penetration level of MicroSilver BG™.**

In vitro testing: Penetration on the oral mucosa – Toothpaste

Protocol — Application of 10 mg/cm² of a toothpaste containing 0.05 % of MicroSilver BG™ on a biopsy of oral mucosa.

Method — Franz diffusion cell. Analysis of the oral mucosa through cryosections and of the receptor liquid 4 hours following application.

Results — Less than 1.3 % of silver is found in the mucuous membrane. No trace of silver was found in the receptor liquid.

☑ **On the whole, there was no significant absorption observed of MicroSilver BG™ or of silver by the oral mucosa after 4 hours.**

Contact allergy

The silver salts may have an astringent (locally corrosive) effect on the skin, like for example, silver nitrate («pierre infernale» or lunar caustic). But it is highly improbable that MicroSilver BG™ releases such amounts of silver ions. No description of any allergy to silver, allergy of the contact type, with silver of a very high purity (such as MicroSilver BG™) was found in the reference literature. If, however, an allergic reaction following application of a product containing MicroSilver BG™ were to occur, it would very probably be caused by other elements in the composition (for example, perfumes or preservatives) or by other impurities.

Formulation aid

As a general rule, MicroSilver BG™ should be added at the end of the manufacturing process, for example, with the O/W or W/O systems, following the emulsification phase. To do this, a suspension mere of MicroSilver BG™ in glycerine is prepared then inserted through shaking until there is a perfect homogeneity. One should make sure that the suspension mere is sufficiently fluid before incorporation in order to prevent the formation of agglomerates. The glycerine concentration in the final product will be approx. 3 to 5 %.

- MicroSilver BG™ is UV resistant
- No temperature limit
- No pH limit

Interactions with other components

MicroSilver BG™ is made of pure elemental silver. Therefore, any interactions with other components are excluded. Nevertheless, minimal quantities of silver ions form in the formulation through oxidation. Certain components may inhibit these silver ions and reduce the efficacy of MicroSilver BG™, in particular, its protective microbiological properties. In this case, the use of classic preservative agents is necessary. In addition, the proteins potentially present in the formula may be modified and lose their functionality through chelation with the silver ions.

! **To minimize such interactions to the extent possible, any substances likely to form a bond with the silver ions should be avoided: salts such as chlorides (e.g. sodium chloride), EDTA or proteins.**

Microbiological protection of the cosmetic formulation

MicroSilver BG™ exerts protective microbiological properties in the product insofar as silver ions may form at any moment in the product when there is the presence of water. This is a secondary positive effect, but not the principal activity of MicroSilver BG™.

We know from experience that:

- MicroSilver BG™ with 0.1 % has a good preservative effect for the formulas of the absorbent creams/milks, gels and lotions type. It is, however, possible that this concentration is not enough to prevent the growth of yeast/fungi. In this case, one should add 0.3 to 0.5 % of benzyl alcohol in order to strengthen the microbiological protection of the formula.

- In principle, where there is a concentration of 0.2 % or higher of MicroSilver BG™, no other preservative agent is necessary. Nevertheless, the proper microbiological protection of each formula should be checked.

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Radhesh Kumar

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Johannes Müller-Steinmann, Ute Goldbach, Stephan Höhn, Alexandra Petukhova, Marcel Langenauer

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Application Study : Cream with Microsilver improves skin condition affected by Neurodermatitis.
STADA GmbH/ Britta Wollnweber

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Adjuvant skin care with a Micro-Silver containing emollient with DMS-lipid-structure. Efficacy and cosmetical acceptance in atopic eczema and psoriasis.
Angela Neub, Ulrich Amon

COSSMA – 3/2009
Antibacterial actives – natural silver for the skin.
Barbara Reinhardt

Pharmaceutical Journal – 4/2009
MicroSilver – An old active substance in new clothes.
Rolf Daniels, Martin Mempel, Martina Ulrich, Peter Steinrücke

BioEpiderm is a German company, created in 2004 as a subsidiary of Bio-Gate AG. Bio-Gate AG is a leading provider of antimicrobial solutions and new products, and is the sole worldwide provider for complete client solutions in the area of silver technologies. The knowledge and expertise developed by Bio-Gate in the production and use of microparticulate silver have been exclusively granted to BioEpiderm for dermatological application in cosmetic and body care products.

History of silver

Silver, or Ag, is derived from the Latin word «argentum». Silver has been worked since around the 5th Century B.C. It was used, for example, by the Assyrians, the Goths, the Greeks, the Romans, the Egyptians and the Germanic peoples. At times, it was considered to be more precious than gold. To the Egyptians in Antiquity, silver was known as «lunar metal».

Cyrus, founder of the Persian Empire in the 5th Century B.C., already drank boiled water from the Choapses River in silver jugs. The pioneers of the American Far West put pieces of silver in their bottles to preserve water or fresh milk.

Carl von Naegeli (1817-1891) was the first to describe, in a scientific manner, the broad-spectrum antimicrobial effect of silver. The stimulating and regenerative properties of lunar metal are used in anthroposophical treatments.

In medicine, silver is used as an antibacterial for dressings as well as for small surgical devices, and even to cover prosthesis. As well, positive silver ions are used as a disinfecting and recommended product for the treatment of wounds.

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