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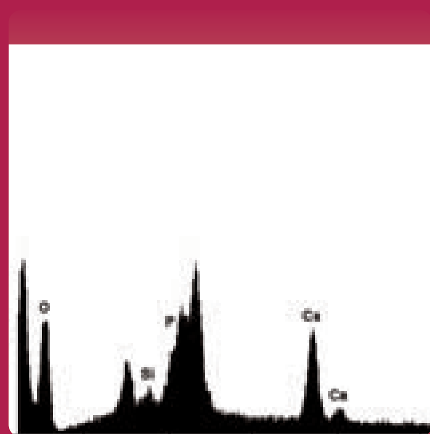

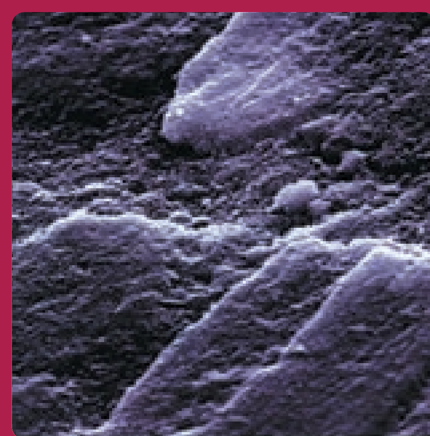

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Bioactive Glasses: A Potential New Class of Active Ingredients for Personal Care Products

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Introduction

Bioactive glasses are known to the biomaterials and medical implant device community mainly as bone grafting materials. Their beneficial biological activity and high level of biocompatibility within the body are well documented in the biomaterials literature (1-3). Recent demonstrations that finely grained powders of bioactive glasses have substantial anti-microbial, anti-inflammatory and mineralizing properties have led to the hypothesis that these may be suited to function as active ingredients for use in a broad variety of cosmetic and personal care products. Some prototype formulations demonstrate that the desired biological activity may be reflected in the end product use.

Medical History

Bioactive glasses were introduced in the 1970's as a novel class of bone implant material (1,2). Designed to have an active, rather than inert, surface chemistry when implanted into the body, bioactive glasses have the ability to build substantial bonds with both hard (bone) and soft (subcutaneous) tissue. This »tissue bonding« response of the body thus contrasts substantively with the encapsulation and eventual rejection of other standard implant materials such as metals and plastics. Implanted into a bone defect, the surface of bioactive glass remodels to form hydroxycarbonate apatite (HCA), the chemical and structural equivalent of bone mineral. In addition, osteoblast activity at the bone repair site is known to be markedly enhanced in the presence of bioactive glasses (1,2) The basic efficacy and biocompatibility in numerous *in vitro* and *in vivo* systems is well documented (1,2). Today, bioactive glasses are marketed worldwide to the implant market for a variety of small osseous defect repair.

Biological Activity of Glass

When considered as a material, glass is a collective term of an unlimited number of different compositions in a glassy or amorphous state. In opposite to crystalline materials glasses do not have a long range order in their molecular network but have a more random network structure.
In the case of inorganic glasses this network is build up by so called network former (e.g. SiO_2,P_2O_5). Further additives which can be included in the glass are called network modifier (e.g. Na_2O, CaO). While constituents and compositional ranges may vary, bioactive glasses are typically composed of oxides of silicon, calcium, sodium and phosphorus. In the form that is approved for medical use, and for which the bulk of safety and efficacy data exists, the composition is 45 %wt SiO_2, 24.5 %wt CaO, 24.5 %wt Na_2O, 6 %wt P_2O_5.
In an aqueous environment a rapid ion exchange between Na^+ out of the glass matrix and H^+ from the water takes place, which is the starting point of a multi step process. This exchange generally leads to an increase in pH of the surrounding solution, which can be substantial for finely grained powders having high surface to volume ratios. The fast release of sodium ions is accompanied by a somewhat slower release of other species like calcium ions, silica and phosphorous. These releases are caused by a very slow dissolution of the glass surface. Under certain conditions in solution, these species will precipitate onto the glass surface and other nearby surfaces, to form calcium and phosphorous containing layers. These surface layers can transform into crystalline HCA. The ability to build such a surface is the reason for the bonding ability to human tissue and can be seen as a measure of the »bioactivity« of the glass.
In the past few years, bioactive glasses in finely grained powder of less than approx. 100 microns have demonstrated biological activities not evidenced from their usage as medical implant materials.

Basic Antimicrobial activity

Bioactive glasses have demonstrated broad-spectrum biocidal activity against a variety of oral and dermal bacteria, as well as against some fungus and yeast species. This activity is strongly pH dependent, decreasing significantly when bioactive glass-containing solutions are buffered towards neutral pH. However, comparisons of the biocidal activity of bioactive glass with a NaOH reference solution appear to indicate a residual effect from the bioactive glass that is independent of pH, as shown in **Table 1**. Bioactive glass shows significant higher minimal inhibition concentrations [MIC] than NaOH with the same pH.
Beside the pH-effect it is well known that the surface charge of inorganic particles have an impact on the viability of microorganisms. The bioactive glass particles normally show a high positive surface charge in an aqueous solution. This can be modified by the specific formulation for example by changing the pH. The isoelectrical point of the glass powder is between a pH of 4 and 5. Further antimicrobial mechanisms can be related to the very high ion release and concentrations especially near the particle surfaces.
The antimicrobial efficacy can also be shown in deodorant application test.

Endconcentration in %	4 (pH 9,1)	3 (pH 8,7)	2 (pH 8,4)	1 (pH 8,2)	0,5 (pH 8,1)	0,25 (pH 7,9)	0,1 (pH 7,8)	MIC in %
Corynebacterium xerosis	–	–	–	–	++	+-	++	1
Eschericia coli	–	–	–	+-	++	++	++	3
Psendomonas aeruginosa	–	–	-+	++	++	++	++	3
Staphylococcus epidermis	–	–	–	–	–	–	++	0,25
Aspergillus niger	–	–	–	–	–	–	++	0,25
Candida albicans	–	–	–	–	–	++	++	0,5
Propionibacterium acnes	–	–	–	++	++	++	++	2

without Bioactive Glass pH of agar	(pH 9,1)	(pH 8,7)	(pH 8,4)	(pH 8,2)	(pH 8,1)	(pH 7,9)	(pH 7,8)	
Corynebacterium xerosis	++	++	++	++	++	++	++	
Eschericia coli	++	++	++	++	++	++	++	
Psendomonas aeruginosa	++	++	++	++	++	++	++	
Staphylococcus epidermis	-+	++	++	++	++	++	++	
Aspergillus niger	–	–	+-	++	++	++	++	
Candida albicans	–	+-	++	++	++	++	++	
Propionibacterium acnes	++	++	++	++	++	++	++	

Table 1 Minimal Inhibition Tests (MIC) – Comparative results of Bioactive Glass and NaOH reference solution at same pH

Fig. 1 shows the result of a sniff test with a non aqueous silicon oil formulations for a concentration of 0,6 wt % bioacitve glass compared to 0,2 % Triclosan. This formulation was especially chosen to show the efficacy of the bioactive glass and avoid any interaction or effects with other ingredients. The test was performed with 22 volunteers (19 female/3 male; age 29 - 64) at the armpits.

The duration and frequency of application was once a day, then twice a day over five days.

Anti-inflammatory activity

Although the mechanism of anti-inflammatory efficacy is currently not completely clarified, finely grained bioactive glass powders have additionally demonstrated the ability to reduce *in vivo* inflammatory responses to both invasive and topical external irritants. This anti-inflammatory property is all the more remarkable given the fact that the pH of immediate environment is alkaline to a degree that would itself normally induce inflammation.

The evaluation of the potential of bioactive glass to decrease the erythemal response from UV irradiation has been performed. **Fig. 2** shows the anti-inflammatory test result with o/w formulations of a lotion (N=7 efficacy test) and a cream (N=25 efficacy test) compared to the same formulation of 5 % aloe vera (10x) and a commercially available cream of 0.5% hydrocortisone. Both test samples of lotion and cream contain ~5% bioactive glass. The results indicate that the bioactive glass significantly reduces erythemal response from post UV irradiation.

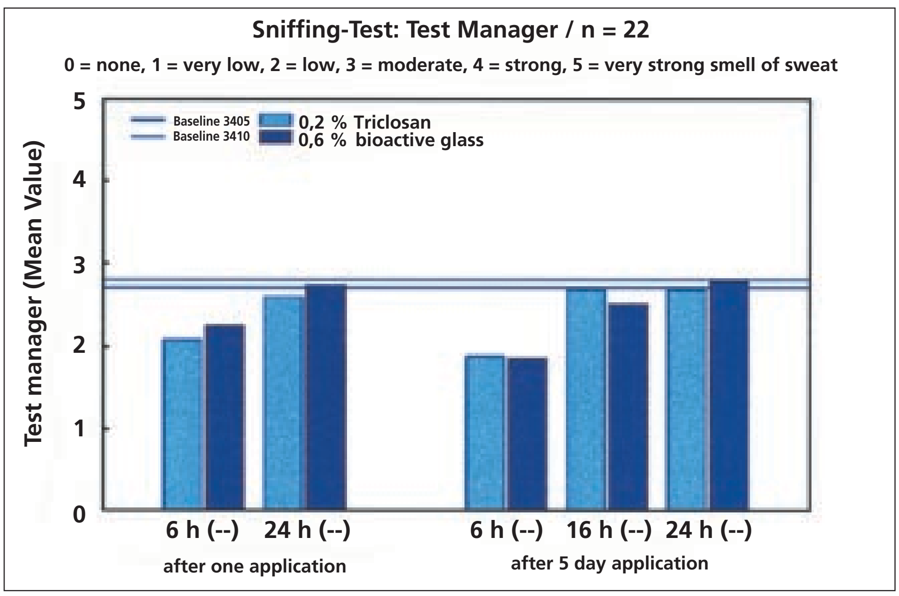

Fig. 1 Efficacy of bioactive glass

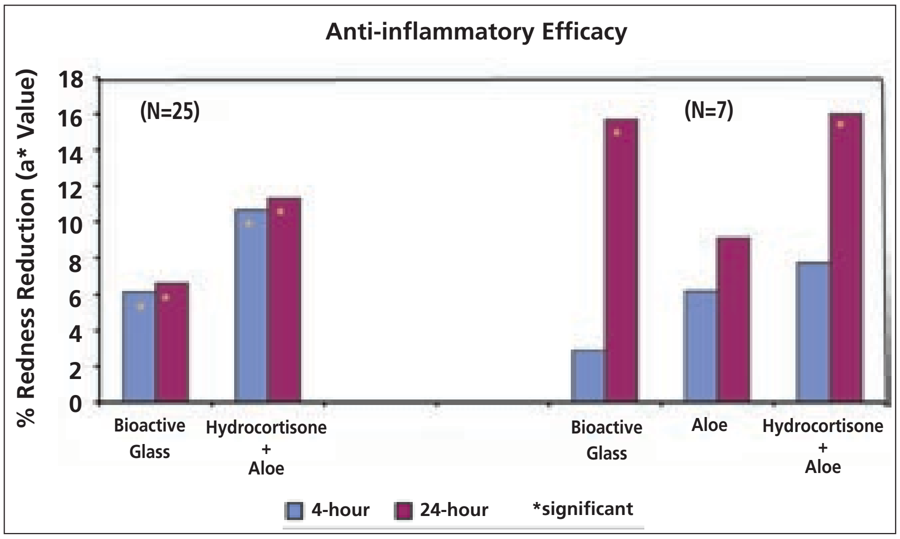

Fig. 2 Anti-inflammatory test result

Mineralisation

The time dependant release of Ca (Ca^{2+}) and phosphorous (PO_4^{3-}) leads to a precipitation of these elements on contact surfaces in aqueous solutions. This leads to the formation of an amorphous Calcium phosphate layer which can crystallize to hydroxycarbonate apatite (HCA). The crystallization effect is concentration dependant and has a maximum in standard aqueous formulations at a concentration of about 1 wt%. The released components can also diffuse through permeable surfaces and enrich in the near surface area. **Fig. 3** shows an SEM image (including EDX) of a precipitation layer on human nails.

Applications in Cosmetics and Personal Care

Because of the active surface chemistry of bioactive glasses, agglomeration can occur readily during product formulation. A new performance active, Engelhard Actysse™ premiere BG (contains Schott Vitryxx™ Bioactive Glass), has been developed to avoid the agglomeration problem. This product, available from Engelhard Corporation, uses mica as a spacer between the bioactive glass particles to improve its dispersibility considerably, thus facilitating

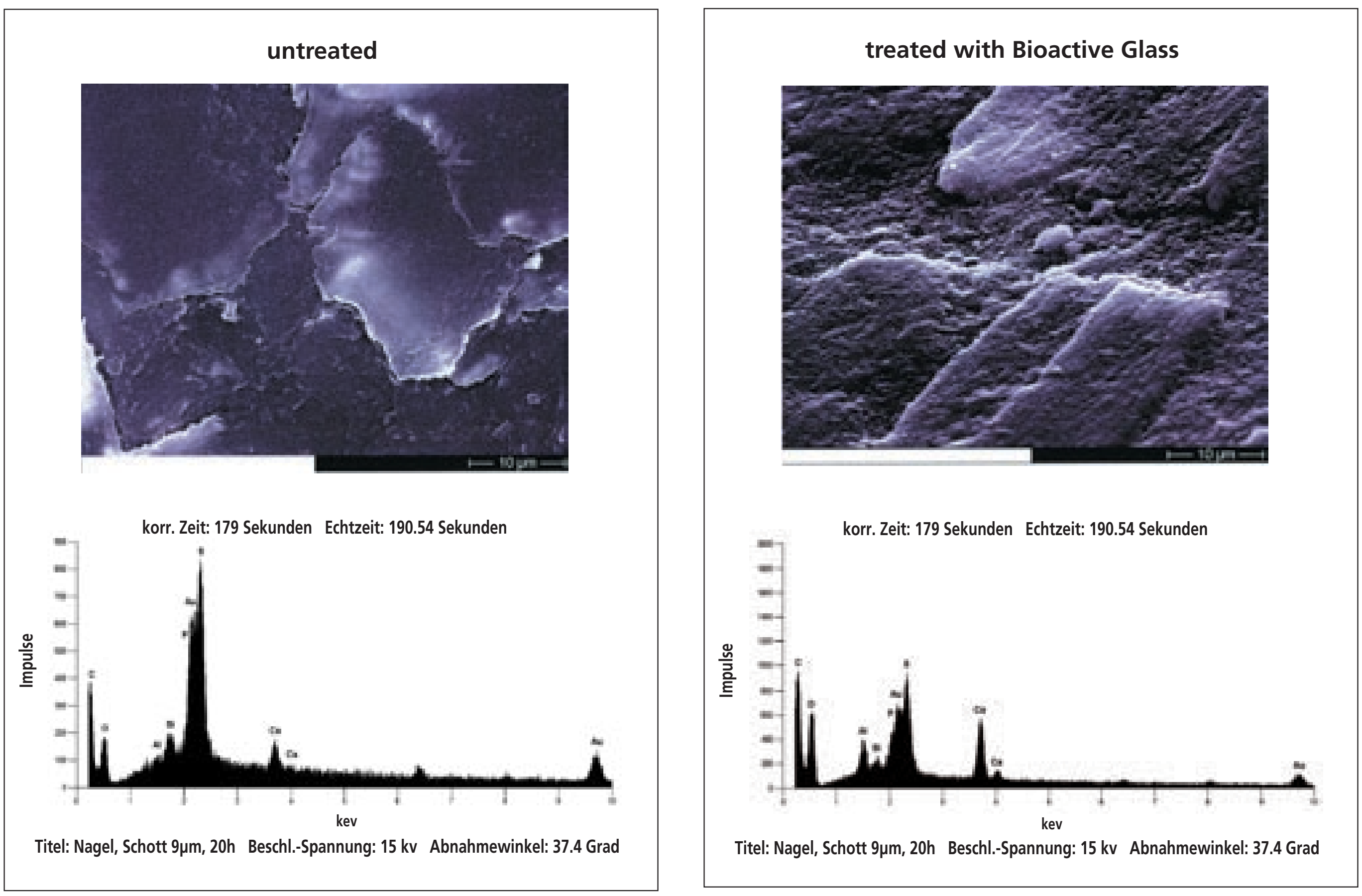

Fig. 3 SEM image (including EDX) of a precipitation layer on human nails

a smooth, lump-free product. Concentrations of Actysse™ premiere BG from 1 % to 5 % are adequate to effect a desirable biological activity.
The high alkaline characteristic is due to ion exchange between Na^+ and H^+ when the bioactive glasses are dispersed into water and is a major challenge for effective formulation. For example, aqueous solutions of 1 % and 5 % bioactive glasses show pH values of 10.5 and 11.5, respectively. When the bioactive glasses are dispersed into water, a substantial amount of ions will be released into the resulting aqueous solution. The combination of high pH and high ion content can deactivate, and thus destabilize the thickening mechanism of lotion/cream formation. Alkali-swellable acrylates copolymers such as Carbopol® produced by Noveon can provide a compatible thickening system to suspend bioactive glasses and stabilize high pH creams/lotions. This is due to the fact that the acrylates copolymer is effective over a broad range of pH's ranging from neutral to high alkaline. Carbopol® Aqua SF-1 is especially suitable for Actysse™ premiere BG as a thickening agent because of its relatively high ion tolerance. Using a thickener with high ion tolerance can eliminate the loss in the thickening efficiency and can maintain the desirable viscosity of the end product.
Using a 5 % Actysse™ premiere BG with variable Acrylates Copolymer concentrations, basic formulations for lotions and creams with different rheologies can be developed, as shown in **Table 2**.
Other thickening systems such as high molecular weight polysaccharide starch derivatives, e.g. Xanthan gum, can be used as a rheology control agents in aqueous systems and as a stabilizers for emulsion and suspensions. Xanthan gum is also compatible with bioactive glasses due to its rheological pH independence and its salt tolerance.
As stated above, aqueous solutions containing bioactive glasses will have the characteristic of a high pH and the presence of significant amounts of ions. Such properties will preclude the use of cationic emulsifiers. Bioactive glasses are generally compatible with nonionic, soap and some anionic agents.
Bioactive glasses can also be dispersed into solvent-based nail enamel systems. However, the high pH system of the bioactive glasses does not allow for effective swelling of the suspending agent, a rheological additives of Hectorite Clay, thus affecting the rheology of the system. Consequently, bioactive glasses and other particulates such as pigments can settle and

% Acrylates Copolymer	Product Characteristics
1.50	Sprayable Lotion
2.25	Lotion
3.00	Flowable Cream
3.75	Non-flowable Cream

Table 2 Basic formulations for lotions and creams

Formulation 1: Facial Cream

Phase	Ingredients	%wt.
A	DI Water	67.25
	Glycerine	2.50
	PPG-2 Myristyl Ether (Crodamol PMP) (1)	2.00
	Cetearyl Octanoate (Crodamol CAP) (1)	3.25
	Jojoba Oil (Lipovol J) (2)	3.00
	Cetyl Alcohol (Crodacol C-70) (1)	1.50
	Ceatearyl Alcohol/Ceteareth-20 (Promulgen D) (3)	3.00
B	Acrylates Copolymer (Carbopol Aqua SF-1) (4)	5.00
C	Cyclomethicone (and) Dimethicone (Dow Corning 1401 Fluid) (5)	2.50
D	Preservatives	q.s.
E	DI Water	5.00
	ActysseTM premiere BG (6)	5.00

(1) Croda, Inc. (2) Lipo Chemicals, Inc. (3) Dow Chemical Company
(4) Noveon (5) Dow Corning Corporation (6) Engelhard Corporation

Formulation 2: Nail Enamel

Phase	Ingredients	%wt.
A	Suspending Lacquer SLF-2 (Butyl Acetate (and) Toluene (and) Nitrocellulose (and) Tosylamide/Formaldehyde Resin (and) Isopropyl Alcohol (and) Dibutyl Phthalate (and) Ethyl Acetate (and) Camphor (and) n-Butyl Alcohol (and) Silica (and) Quaternium-18 Hectorite) (1)	78.00
	Red 7 Lake (4.6% Dispersion in Nitrocellulose Base)	3.00
	Lacquer 127P (Butyl Acetate (and) Toluene (and) Nitrocellulose (and) Tosylamide/Formaldehyde Resin (and) Isopropyl Alcohol (and) Dibutyl Phthalate (and) Ethyl Acetate (and) Camphor (and) n-Butyl Alcohol) (1)	14.00
B	Suspending Lacquer SLF-2 (Butyl Acetate (and) Toluene (and) Nitrocellulose (and) Tosylamide/Formaldehyde Resin (and) Isopropyl Alcohol (and) Dibutyl Phthalate (and) Ethyl Acetate (and) Camphor (and) n-Butyl Alcohol (and) Silica (and) Quaternium-18 Hectorite) (1)	4.00
	Actysse™ premiere BG (1)	1.00

(1) Engelhard Corporation

Formulation 3: Deodorant Stick

Phase	Ingredients	%wt.
A	DI Water	10.00
	Propylene Glycol [1]	58.00
	Castor Oil/IPDI Copolymer (Polyderm PPI-CO-200) [2]	12.00
	Sodium Stearate [1]	8.00
	Isosteareth-2 Alcohol (Dermocol IS-2) [2]	2.00
B	DI Water	5.00
	Actysee™ premiere BG [3]	5.00

[1] Jeen International Corporation [2] Alzo International Inc. [3] Engelhard Corporation

Formulation 4: Hair Styling Gel

Phase	Ingredients	%wt.
A	DI Water	37.00
	Acrylates Copolymer (Carbopol Aqua SF-1) [1]	10.00
	Preservatives	q.s.
B	DI Water	40.00
	Glycerine	5.00
	Actyssee™ premiere BG [2]	5.00
C	AMP-Acrylates (Fixate G-100) [1]	3.00

[1] Noveon [2] Engelhard Corporation

Formulation 5: Lotion

Phase	Ingredients	%wt.
A	Xanthan Gum (Keltrol T) [1]	0.20
	Cellulose Gum (CMC 7LF) [2]	0.20
	DI Water	72.60
B	PEG-7 Glyceryl Cocoate (Cetiol HE) [3]	6.00
	ActysseTM premiere BG [4]	5.00
	Preservatives	q.s.
C	Isopropyl Myristate	2.00
	Oleyl Alcohol (Novol) [5]	6.50
	Mineral Oil (and) Lanolin Alcohol (Amerchol L-101) [6]	4.50
	Cetearyl Alcohol (Lanette O) [3]	2.00
	Stearic Acid	1.00

[1] CP Kelco [2] Hercules Corporation [3] Cognis Corporation
[4] Engelhard Corporation [5] Croda, Inc. [6] Dow Chemical Company

accumulate at the bottom of container. Fortunately, a limited loading of the bioactive glasses does not affect the stability of a nail enamel. It has been determined that a 1 % concentration of Actysse™ premiere BG in a solvent based nail enamel is stable for at least 30 days at an elevated temperature of 45 °C.
Another significant factor for effective formulation is the incorporation technique. The addition sequence of the ingredients and the adequate mixing of the ingredients are critical in the successful formulation of the bioactive glasses. Typically, bioactive glasses are mixed with water first and then the mixture is added to the product formulation at later stages. This order of addition is important in obtaining optimal benefit from the bioactive glasses. Bioactive glasses have demonstrated an excellent gelling ability for emulsion/polymer system. Using high shear homogenisation is also very helpful in creating good emulsions and insuring thorough dispersion of the particles.
As of today, a broad range of cosmetic products has been successfully formulated with bioactive glasses. The products include: Color Cosmetics (e.g. Mascara, Foundation, Eye Shadow, Lipsticks, Pressed Powder Blush), Skin Care (e.g. Facial Cream, Skin Gel), Hair Care (e.g. Conditioner, Styling Gel), Nail Care (e.g. Nail Enamel, Base Coat), Men's Care (e.g. Shave Cream, After Shave Balm), Deodorants (e.g. Stick, Spray), Bath/Cleaning (e.g. Bar Soap, Liquid Soap), etc. These products have passed accelerated stability tests (45 °C at 30 days, 3 cycles of Freeze/Thaw – 24 hours). This demonstrates the long-term (6+ months) shelf life stability of these products. There are few limits on the applications in which bioactive glasses can be utilized (**Formulation 1 – 6)**.
In an effort to determine the efficacy of bioactive glasses following topical application, a number of consumer panel tests have been conducted, and some of the results are summarized:

- **Anti-inflammatory Efficacy Test for Skin**
  A »Facial Cream« **(Formulation 1)** and a »Lotion« **(Formulation 5)** have been tested for attenuation of UV induced erythema. The results of the tests confirm that the test material containing 5 % Actysse™ premiere BG significantly reduces »Erythemal Response« from post UV irradiation.

- **Mineral Enrichment for Nail**
  A lacquer suspension of 1 % Actysse™ premiere BG **(Formulation 2)** has been tested for the efficacy. The results

Formulation 6: After Shave Balm

Phase	Ingredients	%wt.
A	DI Water	32.20
	Glycerine	30.00
	Propylene Glycol (1)	7.50
	Acrylates Copolymer (Carbopol Aqua SF-1) (2)	5.00
	Alcohol C-39	15.00
	Preservatives	0.30
B	DI Water	5.00
	Actysse™ premiere BG (3)	5.00

(1) Jeen International (2) Noveon (3) Engelhard Corporation

indicate that a solvent based nail enamel with bioactive glass exhibits significantly better »Wear« scores.

- Anti-odour Sniff Tests

The sniff test with deodorant stick containing bioactive glasses shows significant efficacy in reducing axillary odor after 8, and even after 24 hours. The sniff test conducted with an antiperspirant stick containing bioactive glasses shows a significant antiperspirant efficacy. The antiperspirant stick containing bioactive glasses demonstrated antiperspirant effect by reducing sweat production by 15 %.

These results show a pattern of promising efficacy in a wide variety of applications, and more tests are planned for the near future in order to establish the full potential of this intriguing material.

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