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(54) **Title**: FORMULATION BASED ON MICRONIZED CLINOPTILOLITE AS THERAPEUTIC AGENT PROVIDING HIGHLY BIOAVAILABLE SILICON

$$(Me^{n+})_{x/n}[(AlO_2)_x(SiO_2)_y]\bullet mH_2O\ (\mathbf{MC})$$

(57) **Abstract**: This invention relates to a formulation based on micronized clinoptilolite (MC) as therapeutic agent for effective release of highly bioavailable silicon. The formulation comprising variable portions of: (i) micronized clinoptilolite (MC) of general formula: $(Me^{n+})_{x/n}[(AlO_2)_x(SiO_2)_y]$-$mH_2O$ (MC) where Me= H, Li, Na, K, Mg, Ca, Zn, Ag, Cu, Mn, Fe; whereas ratio of silicon to aluminum, y:x is between 2.6:1 to 5: 1; number of crystalline water m is from 0 to 20, which is characterized by particles size from 500 nm to 5 μm; and of (ii) one or more excipients which yield in desired pharmaceutical form: tablets, capsules, ointments, creams, gels, lotions, shampoos, powders, liquid powders, compact powders, masks, suppositories, syrups, suspensions, soaps, and therapeutic patches; and of one or more pharmaceutical or cosmetic active substances which contribute and/or enhance basic biological actions of silicic acid. The use of the formulation provides all known positive therapeutic effects of highly bioavailable silicon: stimulation of immune system; treatment of allergic conditions; adjuvant terapy at microbial infections; increasing strength of blood vessels walls, and decreasing of their wall permeability; stimulation of joints and ligaments functions; stimulation of osteoblasts and bone mineralizations; prevention of osteoporosis; decreasing resorption of aluminum from gastrointestinal tract; improving structure of cartilage; antiinflammatory action at various acute or chronic inflammatory diseases; treatment of various skin diseases such as skin irritations, ekzema, seborrheic dermatitis, neurodermitis, atopic dermatitis, psoriasis; treatment of decubitus; treatment of wounds and burns; stimulation of biosynthesis of collagen and elastin; slowing down of skin ageing; reduction of wrinkles; stimulation of hair growth, strength, and brightness; and stimulation of nails growth and strength.

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FORMULATION BASED ON MICRONIZED CLINOPTILOLITE AS THERAPEUTIC AGENT PROVIDING HIGHLY BIOAVAILABLE SILICON

DESCRIPTION

THE FIELD OF THE INVENTION

The present invention relates to a formulation based on micronized clinoptilolite which is used as efficient therapeutic agent for providing highly bioavailable silicon. The formulation is used for treatment of various disorders and diseases which are cured with biologically available silicon.

THE SUMMARY OF THE INVENTION

The present invention solves technical problem of improved pharmaceutical or cosmetic product which provides highly bioavailable silicon, based on formulation consisting of variable portions of:

(i) micronized clinoptilolite (**MC**) of general formula:

$$(Me^{n+})_{x/n}[(AlO_2)_x(SiO_2)_y]\bullet mH_2O \text{ (MC)}$$

wherein Me= H, Li, Na, K, Mg, Ca, Zn, Ag, Cu, Mn, Fe; whereas ratio of silicon to aluminum, y:x is between 2.6:1 to 5:1; number of crystalline water *m* is from 0 to 20, which is characterized by particles size from 500 nm to 5 μm; and of

(ii) one or more excipients which yield in desired pharmaceutical form: tablets, capsules, ointments, creams, gels, lotions, shampoos, powders, liquid powders, compact powders, masks, suppositories, syrups, suspensions, soaps, and therapeutic patches; and of one or more pharmaceutical or cosmetic active substances which contribute and/or enhance basic biological actions of silicic acid.

The formulation from the present invention exhibits all positive therapeutic effects of bioavailable silicon when applied in human or animal organism.

PRIOR ART

Silicon is important essential microelement with a number of roles in human or animal organism. Biologically available form of silicon is ortho-silicic acid (H_4SiO_4). The latter exhibits several useful biological effects:

(i) Stimulation of immune system [A. Schiano, F. Eisinger, P. Detolle: Silicium, tissu osseux et immunité, *Revue du Rhumatisme* **46** (1979) 483];

(ii) By stimulating of immune system it enhances natural ability of organism to fight against microorganisms, and with other disorders and diseases which occur in cases of weakened immune system, e.g. various allergic diseases [W. A. Kros, U.S. 2006/0178268 A1];

(iii) Takes a part in the structure of arterial, veins, and capillary walls; increases elasticity and hardeness of blood vessels, decreased their permeability;

(iv) It is a cross-linking agent for glycosaminoglycans and mucopolysaccharides in joints and ligaments [K. Schwartz: A bound form of silicon in glycosaminoglycans and polyuronides, *Proc. Nat. Acad. Sci. USA* **70** (1973) 1608; A. Lassus: Colloidal silicic acid for the treatment of psoriatic skin lesions, arthropathy and onychopathy. A pilot study. *J. Int. Med. Res.* **25** (1997) 206];

(v) Helps resorption of calcium; involved in its transport; stimulates osteoblasts and bone mineralization; promotes bone healing; helps in osteoporosis prevention [E. M. Carlisle: A requirement for silicon for bone growth in culture, *Fed. Proc.* **37** (1978) 1123; E. M. Carlisle: A relation between silicon and calcium in bone formation, *Fed. Proc.* **29** (1970) 265; E. M. Carlisle: Silicon: a requirement in bone formation independent of vitamin D, *Calcif. Tissue Int.* **33** (1981) 27; D. M. Reffitt, N. Ogston, R. Jugdaohsingh: Orthosilicic acid stimulates collagen type I synthesis and osteoblast-like cells *in vitro*, *Bone* **32** (2003) 127; S. Spripanyakorn, R. Jungdaohsingh, R. P. H. Thompson, J. J. Powell: Dietary silicon and bone health, *Nutr. Bull.* **30** (2005) 222];

(vi) In oligomeric form, silicic acid decreases resorption of aluminum from gastrointestinal tract, thus beside antioxidative action, preventively influences on development of neurodegenerative diseases like Alzheimer's disease [J. D. Birchall, J. S. Chappell: The chemistry of aluminium and silicon in relation to Alzheimer's disease, *Clin. Chem.* **34** (1980) 265; R. Jugdaohsingh: Soluble silica and aluminium bioavailability, PhD Thesis (1999) University of London; R. Jugdaohsingh, S. H. Anderson, K. L. Tucker: Dietary silicon intake and absorption, *Am. J. Clin. Nutr.* **75** (2002) 887; R. Jugdaohsingh, D. M. Reffitt, C. Oldham: Oligomeric but not monomeric silica prevents aluminium absorption in human, *Am. J. Clin. Nutr.* **71** (2000) 944; D. M. Reffitt, R. Jugdaohsingh, R. P. H. Thompson: Silicic acid: its gastrointestinal uptake and urinary excretion in man and effects on aluminium excretion, *J. Inorg. Biochem.* **76** (1999) 141];

(vii) Takes a part in the structure of cartilage: Formation of functional tertiary structure of building proteins like elastin in soft organs such as liver, lung and brain [E. M. Carlisle, D. L. Garvey: The effect of silicon on formation of extra-cellular matrix components by chondrocytes in culture, *Fed. Proc.* **41** (1982) 461; E. M. Carlisle, C. Suchil: Silicon and ascorbate interaction in cartilage formation in culture, *Fed. Proc.* **42** (1983) 398];

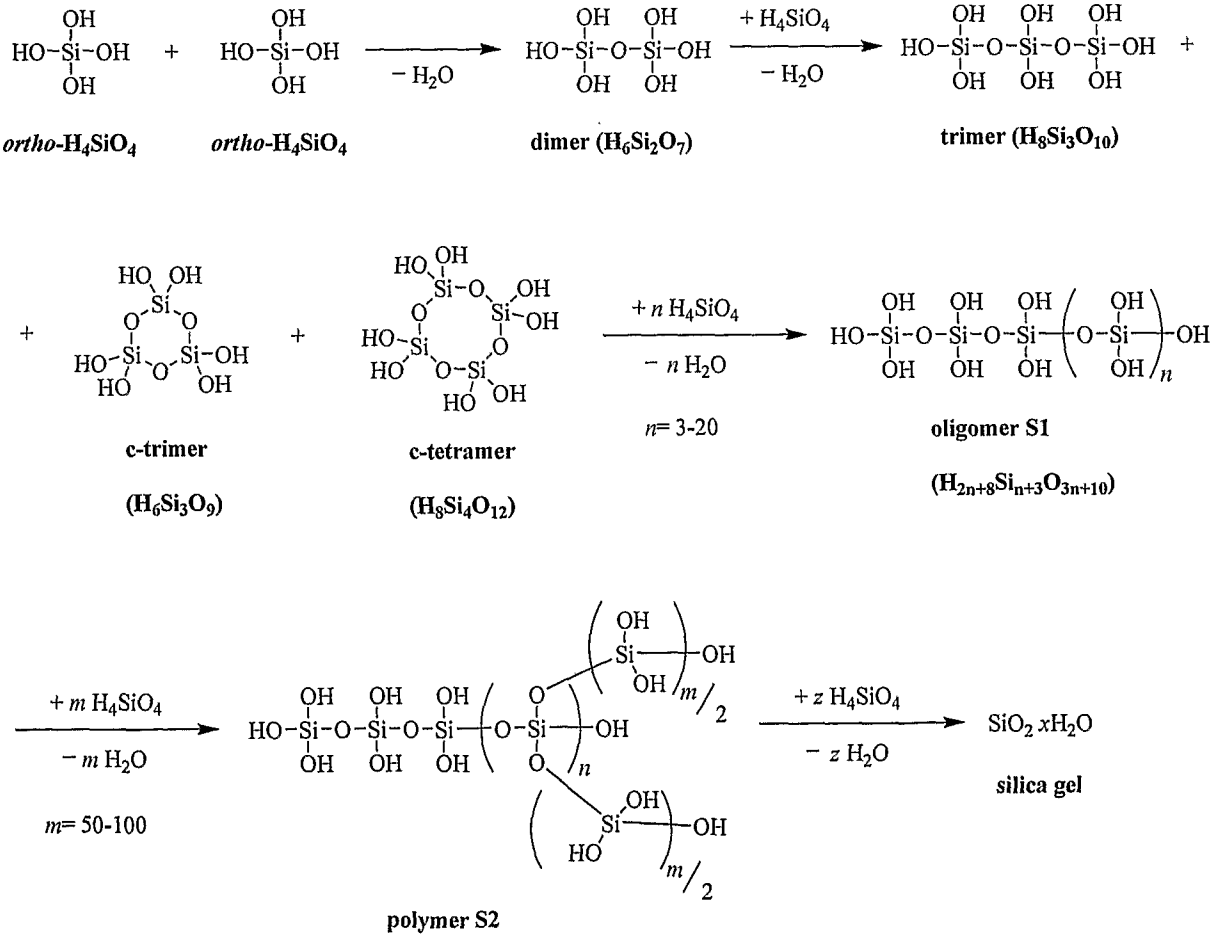
(viii) Exhibits antiinflammatory action in the cases of various skin disorders and diseases such as: psoriasis; seborrheic dermatitis; neurodermitis; atopic dermatitis; skin irritations; disorders connected with decubitus; accelerates wound healing; and several other skin disorders [A. Lassus: Colloidal silicic acid for oral and topical treatment of aged skin, fragile hair and brittle nails in females, *J. Int. Med. Res.* **21** (1993) 209; A. Lassus: Colloidal silicic acid for the treatment of psoriatic skin lesions, arthropathy and onychopathy. A pilot study. *J. Int. Med. Res.* **25** (1997) 206];

(ix) Stimulates biosynthesis of skin building proteins collagen and elastin [C. D. Seaborn, F. H. Nielsen: Silicon deprivation decreases colagen formation in wounds and bone, and ornithine transaminase enzyme activity in liver, *Biol. Trace Element Res.* **89** (2002) 251; M. R. Calomme, D. A. V. Berghe: Supplementation of calves with stabilised orthosilicic acid effect on the Si, Ca, Mg and P concentration in serum and the collagen concentration in skin and cartilage, *Biol. Trace Element Res.* **56** (1997) 153]; and

(x) Stimulates growth of hair and nails [A. Lassus: Colloidal silicic acid for oral and topical treatment of aged skin, fragile hair and brittle nails in females, *J. Int. Med. Res.* **21** (1993) 209].

It is known to those skilled in the art that silicic acid in its monomeric, ortho-form (H_4SiO_4) is of limited stability in aqueous solutions. Silicic acid undergoes polymerization leading to formation of corresponding dimer ($H_6Si_2O_7$), trimer ($H_8Si_3O_{10}$), cyclic oligomers (c-trimer, $H_6Si_3O_9$; c-tetramer, $H_8Si_4O_{12}$), and linear unbranched oligomers (**S1**) which are also water soluble. These linear chain polymers (**S1**) are subjected to further polymerization accompanied with generation of opalescent gel consisting of tridimensional branched polymers (like **S2**) which are not of significant water solubility. The polymerization process proceeds further yielding hydrated silicon dioxide (silica gel; $SiO_2 \cdot xH_2O$). The polymerization pathway of silicic acid is schematically given on Scheme 1.

Scheme 1



Ortho-Silicic acid (H_4SiO_4) and eventually its lower oligomers are sources of highly bioavailable silicon. Branched polymers of silicic acid are not biologically available [H. Yokoi, S. Enomoto: Effect of degree of polymerization of silicic acid on the gastrointestinal absorption of silicate in rats, *Chem. Pharm. Bull.* **27** (1979) 1733; K. Van Dyck, R. Van Cauwenbergh, H. Robberecht: Bioavailability of silicon from food and food supplements, *Fresenius J. Anal. Chem.* **363** (1999) 541].

By using natural and carefully selected food (e.g. whole grain cereals) people usually intake sufficient amounts of silicon. However, at eating strongly processed unhealthy food, silicon deficiency often occurs. Such conditions, eventually accompanied with other factors, often cause several disorders or diseases wherein silicon plays an important roles.

Because of this reason, it is very important to develop reliable source of highly bioavailable silicon for use as food supplement to prevent or to treat mentioned disorders and/or diseases.

There are some formulations based on stabilized silicic acid described in the prior art. As stabilizers of silicic acid in aqueous solution, the following compounds have been used: polyethyleneglycol, polysorbates, vegetable gums, cellulose derivatives, polypropyleneglycols, pectin, higher fatty acids ethoxylates, acetylated or hydroxypropyl-derivatized starches, starch phosphate, urea, sorbitol, maltitol, some vitamins [W. A. Kros, U.S. 2006/0178268 A1]; choline chloride [S. R. Bronder, U.S. 5,922,360 (1999); V. Berghe, D. A. Richard, E.P. 1 371 289 A1 (2002); both to Bio Pharma Sciences B.V.]; and aminoacids such as proline, serine, lyzine, arginine, glycine, polypeptides or protein hydrolysates [V. Berghe, D. A. Richard, WO 2004/016551 A1 (Bio Pharma Sciences B.V.)].

Additionally it is known to those skilled in pharmacognosy that somewhat effective (bioavailable) sources of silicic acid are various plant drugs such as Field Horsetail (*Equisetum arvense*), Lungworth (*Pulmonaria officinalis*), Common Knotgrass (*Polygonum aviculare*), Couch Grass (*Agropyron repens*), Common Agrimony (*Agrimonia eupatoria*), Oat (*Avena sativa*), Dandelion root (*Taraxaci radix*), Nettle (*Urtica dioica*). However, it is known that „soluble" portion of silicic acid in these medicinal plants usually do not exceed 1/10 of its total content. All additional portion of silicic acid present is not soluble and therefore not

biologically available [D. Kuštrak: *Farmakognozija i fitofarmacija*, Golden marketing-Tehnička knjiga, Zagreb (2005)].

Anyway, it is not clear from the prior art what is actual content of highly bioavailable monomeric, ortho-silicic acid (H_4SiO_4) in all these silicon-based products. Since reported biological effects of these products significantly vary, presumably main portion of silicon (Si) present is exisiting in oligomeric, poorly bioavailable forms. Because of this, several products with relatively high nominal contents of silicon (Si) obviously do not exhibit expected pharmacological responses.

Moreover there are some evidences that excessive doses of silicic acid can cause damage of liver and kidneys. The latter are the most important organ for silicon elimination from the organism [J. W. Dobbie, M. J. Smith: Silicate nephrotoxicity in the experimental animal: the missing factor in analgesic nephropathy, *Scotish Med. J.* **27** (1982) 10; H. C. Gonick, F. K.-Manesh, E. W. J. Weiler, U.S. 4,962,127 (1990)]. This fact makes silicon dosage management even more complicated. So, the best manner of silicon dosage is to ensure constant small dosage (μgs/kg of body weight) of bioavailable silicon (as H_4SiO_4), but not in excessive doses (mgs/kg of body weight).

Zeolites are a class of aluminosilicates of general formula:

$$(Me^{n+})_{x/n}[(AlO_2)_x(SiO_2)_y]\bullet mH_2O$$

where Me is usually Na, K, Mg, and Ca but can be also other metal cation; whereas ratio of silicon to aluminum, y:x is between 1:1 to > 10:1; number of crystalline water *m* is from 0 to >100.

Zeolites have numerous technical applications which are mainly based on their strong adsorptive, absorptive, and ion-exchange properties.

It is described in veterinary literature that zeolite A do act as agent for supplementing silicon in animal food [study with calves: K. K. Turner, B. D. Nielsen, C. I. O'Connor-Robison, D. S. Rosenstein, B. P. Marks, F. H. Nielsen, M. W. Orth: Sodium Zeolite A Supplementation and Its Impact on the Skeleton of Diary Calves, *Biol. Trace. Element Res.* **121** (2008) 149-159;

study with horses: K. J. Lang, B. D. Nielsen, K. L. Waite, J. Link, G. M. Hill, M. W. Orth: Increased plasma silicon concentrations and altered bone resorption in response to sodium zeolite A supplementation in yearling horses, *J. Equine Vet. Sci.* **21** (2001) 550-555].

However, the use of zeolite A as silicon source in humans is not acceptable because this kind of zeolite undergo significant release of aluminum too. It is known from the prior art that Alzheimer's patients have increased brain concentration of aluminum. Although there is no clear evidence that increased aluminum intake do directly causes Alzheimer disease, certainly there is significant connection between aluminum and Alzheimer disease [among numerous papers, for example see: T. Flaten: Aluminum as a Risk Factor in Alzheimer's Disease, with an Emphasis on Drinking Water, *Brain Res. Bull.* **55** (2001) 187-196; V. Rondeau: A Review of Epidemiologic Studies on Aluminum and Silica in Relation to Alzheimer's Disease and Associated Disorders, *Rev. Environ. Health* **17** (2002) 107-121]. Therefore, zeolite A as potential silicon source is highly disfavourable because of aluminum which is also released from this kind of zeolite.

Presumably the molar ratio of silicon to aluminum (Si:Al) in zeolite A (Si:Al= 1) is responsible for its high aluminum releasing capacity.

In cosmetic and medicine, only zeolite clinoptilolite [e.g. $Me_2Al_2Si_7O_{18}$, Me= Na, K, or $Me'Al_2Si_7O_{18}$, Me'= Mg, Ca] is employed. The latter is active pharmaceutical substance for treatment of diarrhea (Enterex), wounds, and for detoxification. Clinoptilolite has been studied as adjuvant in anti-cancer therapy [K. Pavelić, *Medical News* **26** (1998) 21-22].

In contrast to zeolite A, clinoptilolite is characterized by completely different basic aluminosilicate structure with molar Si:Al ratio from 2.6-5. Obviously due to two-to-five times lower aluminum content, the healthy problems connected with aluminum intake have not been detected in the cases of clinoptilolite use in humans.

Preparation of micronized clinoptilolite (**MC**) on similar but not identical manner like in this invention was described in prior art [T. Lelas, EP 1316530 (2004); J. R. McLaughlin, US 5,704,556 (1998)]. Alternatively, it can be obtained by wet micronization [T. J. C. Arts, T. J. Osinga, EP 0 823 884 (1996)].

Technical problem of effective release of highly bioavailable silicon by the present invention is solved on a new and more efficient manner by micronized clinoptilolite formulation as will be demonstrated in detailed description of the invention.

DETAILED DESCRIPTION OF THE INVENTION

Preparation, characterization and properties of micronized clinoptilolite (MC)

The present invention relates to the formulation consisting of variable amounts of:

(i) micronized clinoptilolite (**MC**) of general formula:

$$(Me^{n+})_{x/n}[(AlO_2)_x(SiO_2)_y]\bullet mH_2O \text{ (MC)}$$

wherein Me= H, Li, Na, K, Mg, Ca, Zn, Ag, Cu, Mn, Fe; whereas ratio of silicon to aluminum, y:x is between 2.6:1 to 5:1; number of crystalline water *m* is from 0 to 20, which is characterized by particles size from 500 nm to 5 μm; and of

(ii) one or more excipients which yield in desired pharmaceutical form: tablets, capsules, ointments, creams, gels, lotions, shampoos, powders, liquid powders, compact powders, masks, suppositories, syrups, suspensions, soaps, and therapeutic patches; and of one or more pharmaceutical or cosmetic active substances which contribute and/or enhance basic biological actions of silicic acid.

The formulation solves technical problem of improved pharmaceutical or cosmetic product which acts as an efficient source of highly bioavailable silicon (Si) with the use at following applications:

(i) for stimulation of immune system;

(ii) for treatment of allergic diseases;

(iii) as supportive agent for fight against microorganisms like fungi, bacteria, and viruses;

(iv) for enhancement of arterial, veins, and capillary walls; enhancement of elasticity and rigidity of blood vessels; and for decreasing of their wall permeability;

(v) for enhancement of joints, ligaments, and cartilage structures;

(vi) for stimulation of bone mineralization; acceleration of bone healing; prevention of osteoporosis;

(vii) for decreasing of aluminum resorption from gastrointestinal tract and thus prevention of Alzheimer's disease;

(viii) for treatment of various skin disorders and diseases such as: psoriasis; seborrheic dermatitis; neurodermitis; ekzema; skin iritations; atopic dermatitis; skin burns; wound healing; decubitus conditions; dandruff; etc.;

(ix) for stimulation of collagen and elastin biosynthesis; for treatment of wrinkles; and for regeneration of skin;

(x) for prevention of hair loss and for stimulation of hair growth; and

(xi) for stimulation of nails growth.

According to the present invention, micronized clinoptilolite (**MC**) was obtained by micronization of natural clinoptilolite (**C**) which was mainly in calcium form (mainly $CaAl_2Si_7O_{18}$).

Alternatively natural clinoptilolite (**C**) was converted to any of other metal derivatives according to the following general route:

(i) by treatment of natural clinoptilolite (**C**) with suitable acid affording hydrogen (acidic) form of clinoptilolite (**H-C**); and then by

(ii) treatment of such prepared hydrogen form of clinoptilolite (**H-C**), or by treatment of synthetic sodium or potassium clinoptilolite, with solution of suitable metal salt of lithium,

sodium, potassium, magnesium, calcium, zinc, copper, silver, manganese, or iron affording desired metal form of clinoptilolite, **Me-C** where Me= Li, Na, K, Mg, Ca, Zn, Cu, Ag, Mn, Fe.

The conversion of natural clinoptilolite (**C**) is performed by treatment with 2-10 molar equivalents of acids which forms corresponding calcium salts of high water solubility. During this treatment, calcium cations from aluminosilicate structure of clinoptilolite undergo exchange process with hydrogen cations. Acidic form of clinoptilolite (**H-C**) is isolated by filtration, whereas excess of acid is removed by washings. Suitable acid is selected from the group consisting of hydrochloric acid, hydrobromic acid, hydroiodic acid, nitric acid, formic acid, acetic acid, benzenesulfonic acid, *p*-toluenesulfonic acid, methanesulfonic acid, or mixtures of these acids.

The conversion of acidic form of clinoptilolite (**H-C**) to desired metal form of clinoptilolite is carried out by mixing of these materials with aqueous solution of suitable metal salt consisting of halogenides, nitrates, acetates, perchlorates, or arylsulfonates of general formula MeX, $Me'X_2$ or $Me''X_3$; where Me= Li, Na, K, Cu, Ag; Me'= Mg, Ca, Zn, Cu, Mn, Fe; Me''= Fe; X= Cl, Br, I, NO_3, CH_3COO, ClO_4, or $ArSO_3$ such as *p*-$CH_3C_6H_4SO_3$. It is clear to those skilled in the art that in this phase, other water soluble metal salts can also be used.

Since clinoptilolite can be effectively prepared by synthetic methods, the material of synthetic origin can also be employed in this invention [for example see Y. Goto: Synthesis of Clinoptilolite, *Am. Mineralogist* **62** (1977) 330-332].

Then natural clinoptilolite (**C**), semi-synthetic, or synthetic clinoptilolites (**Me-C**) were subjected to micronization process. The micronization process used in the present invention is almost identical with the process (and device) already disclosed in: T. Lelas, EP 1316530 (2004). In our enhanced variant of microniser, the blades geometry was modified leading to enhanced collision occurrence.

We have found that thus obtained micronized clinoptilolites (both **MC** and **Ca-MC**, and others), were of very fine level of particles size ranging from 100 nm to 2 μm with Gauss-type of particles size distribution, and of high range of mesoporosity.

Unexpectedly, we have found that both clinoptilolite (**C**), and more effectively, micronized clinoptilolite (**MC**), under physiological conditions, even at neutral pH value (pH= 7) does act as an effective source of soluble, and thus bioavailable silicon (Si).

Presumably this silicon (Si) is existing in neutral aqueous solution at pH around 7 as silicic acid (H_4SiO_4), as its oligomers ($H_6Si_2O_7$; etc.), and eventually as silicate anions (SiO_4^{4-}; SiO_3^{2-}; in minor concentrations). Since it is well known from the prior art that only these forms possess high bioavailability [H. Yokoi, S. Enomoto: Effect of Degree of Polymerization of Silicic Acid on the Gastrointestinal Absorption of Silicate in Rats, *Chem. Pharm. Bull.* **27** (1979) 1733-1739], micronized clinoptilolite (**MC**) was found to be very effective source of highly bioavailable silicon suitable for production of various pharmaceutical and cosmetic products.

The study of releasing of silicon (Si) from micronized clinoptilolite (**MC**) was performed by stirring the samples (20.00 g) of **MC** in double distilled water (100 mL) for 1 h, and overnight (for 16 h). For comparison, samples of starting, ordinarily milled natural clinoptilolite (**C**) of particle size ranging from 10-100 μm were also tested in the same manners. Then, suspended zeolites were removed by filtration and obtained filtrates were diluted to 100 mL with distilled water, and analysed by atomic absorption spectroscopy (AAS). From thus obtained results, the contents of silicon (Si) as well as corresponding equivalent amounts of silicic acid (calculated as H_4SiO_4) released from 1.00 g of the samples were calculated. Results are given in Table 1.

In all experiments, only high-density polyethylene flasks and equipments were employed in order to exclude traces of silicon which might be released from glassware equipments. Additionaly the content of silicon (Si) in employed sample of double-distilled water was analysed and calculated in this study (through the blank entries).

Table 1. Results of quantitative atomic absorption spectroscopy (AAS) analyses of release of silicon (Si) from samples of clinoptilolite (**C**) and micronized clinoptilolite (**MC**).[1]

Entry	Sample	Conditions[2]	Amount of Si (mg) released from 1.00 g of sample	Calculated amount of H_4SiO_4 (mg) released from 1.00 g of sample[3]
1	**C**	1 h / r. t.	0.110[4]	0.376
2	**MC**	1 h / r. t.	0.130[4]	0.445
3	**C**	16 h / r. t.	0.146[4]	0.499
4	**MC**	16 h / r. t.	0.177[4]	0.607

[1] Determined by quantitative AAS analyses of aqueous supernatants (100 mL) obtained by trituration of samples of clinoptilolites (**C** and **MC**; 20.00 g) at room temperature for 1 h and 16 h.

[2] The term room temperature (r. t.) means the temperature interval: 20-25 °C.

[3] Calculated from amount of released silicon. Expressed as amount of H_4SiO_4 by weight (mg).

[4] The results of repeated experiments were of acceptable reproducibility (oscillations of results were under 3%).

According to these results, clinoptilolite (**C**) acts as effective silicon (Si) releasing agent under ambient conditions (room temperature) in neutral water, indeed. Moreover, micronized clinoptilolite (**MC**) exhibits even more profound action since +18% to +21% increasing of the silicon releases were observed.

Thus obtained results also showed that approximately 73-75% of overall silicon (Si) is released from the parent clinoptilolite samples within relatively short period of time (1 h), whereas the rest of silicon (25-27%) is released during additional 15 h.

Presumably this enhanced releasing potential of micronized clinoptilolite (**MZ**) comes from both increased total surface area (BET method with nitrogen), and increased mesoporosity of this material prepared by micronization according to the method known in the art [T. Lelas, EP 1316530 (2004)].

Probably the main advantage of clinoptilolite as silicon source over other forms known in the art is in its property to release monomeric, ortho-silicic acid (H_4SiO_4). Although the silicon

releasing capacity of clinoptilolite is relatively low, this monomeric, ortho-silicic acid form is crucial for its high bioavailability.

Moreover thanks to this fact, the use of clinoptilolite as the silicon source obviously avoids potential occuring of unwanted side-effects of high dosages forms of silicon. Thus eventual hepatotoxicity can be practically excluded in the case of the use of clinoptilolite as the silicon source.

Although the common knowledge from basic inorganic chemistry (zeolite chemistry) that zeolites do undergo cleavage reaction in acidic medium releasing silicon [R. L. Hartman, H. S. Fogler: Understanding the Dissolution of Zeolites, *Langmuir* **23** (2007) 5477-5484; see also the Application of Euremica Environmental Ltd. for the use of clinoptilolite as novel food: http://acnfp.gov.uk/assess/fullapplics/clinoptilolite] it is not obvious from the prior art that clinoptilolite can act as such effective silicon releasing agent under very mild conditions and neutral pH medium (room temperature / neutral water / pH= 7). The only thing that would be expectable to the person skilled in the art is releasing of exchangeable cations (e.g. Na^{+}, Ca^{2+}, Mg^{2+} etc.) from clinoptilolite micro-pores in neutral water (pH= 7), but not releasing of silicon as silicic acid.

Additionaly, in contrast to zeolite A which is capable of releasing dangerous amounts of aluminum [V. Rondeau, D. Commenges, H. Jacqmin-Gadda, J.-F. Dartigues: Relation between aluminum concentrations in drinking water and Alzheimer's disease: an 8-year follow-up study, *Am. J. Epidemiol.* **152** (2000) 59-66], clinoptilolite is completely safe for long-term applications in humans [A. R. Elmore: Final report on the safety assessment of aluminum silicate, calcium silicate, magnesium aluminum silicate, magnesium silicate, magnesium trisilicate, sodium magnesium silicate, zirconium silicate, attapulgite, bentonite, Fuller's earth, hectorite, kaolin, lithium magnesium silicate, lithium magnesium sodium silicate, montmorillonite, pyrophyllite, and zeolite, *Int. J. Toxicol.* **22** (2003) 37-102.; I. Martin-Kleiner, Z. Flegar-Meštrić, R. Zadro, D. Breljak, S. Stanović-Janda, R. Stojković, M. Marušić, M. Radačić, M. Boranić: The Effect of the Zeolite Clinoptilolite on Serum Chemistry and Hematopoiesis in Mice, *Food Chem. Toxicol.* **39** (2001) 717-727].

In this manner the formulation of the present invention provides a simple, effective, and safe solution of the complicated technical problem of silicon supplementation.

Composition of the formulation according to the invention

The formulation of the present invention is consisting of variable portions of:

(i) micronized clinoptilolite (**MC**) of general formula:

$$(Me^{n+})_{x/n}[(AlO_2)_x(SiO_2)_y]\bullet mH_2O \text{ (MC)}$$

wherein Me= H, Li, Na, K, Mg, Ca, Zn, Ag, Cu, Mn, Fe; whereas ratio of silicon to aluminum, y:x is between 2.6:1 to 5:1; number of crystalline water *m* is from 0 to 20, which is characterized by particles size from 500 nm to 5 μm; and of

(ii) one or more excipients which yield in desired pharmaceutical form: tablets, capsules, ointments, creams, gels, lotions, shampoos, powders, liquid powders, compact powders, masks, suppositories, syrups, suspensions, soaps, and therapeutic patches; and of one or more pharmaceutical or cosmetic active substances which contribute and/or enhance basic biological actions of silicic acid.

The formulation of the present invention is consisting of mentioned components in the following portions:

(i) micronized clinoptilolite (**MC**): from 1.0% to 99.99%;

(ii) one or more excipients, and one or more pharmaceutical or cosmetic active substances: from 0.01% to 99.00%.

The excipients are selected from the group consisting of: fillers; binders; disintegrants; lubricants; emollients; emulsifiers; tensides; humectants; solvents; thickeners; preservatives; antioxidants; stabilizers; and others.

In solid dosage forms such as tablets, fillers are selected from the group consisting of: microcrystalline cellulose; lactose monohydrate; calcium hydrogenphosphate; sorbitol; starch; modified starches; etc. As fillers in powders, liquid powders, and compact powders, the

following substances can be used: talc; kaolin; bentonite; montmorillonite; precipitated calcium carbonate; basic magnesium carbonate; calcium silicate; aluminum hydroxide; silicon dioxide; or mixtures of these substances.

In solid dosage forms, binders are selected from the group consisting of: gelatin; lactose monohydrate; sorbitol; saccharose; xylitol; maltitol; starch; modified starches; methylcellulose; 2-hydroxyethylcellulose; 2-hydroxypropylcellulose; sodium carboxymethylcellulose; polyethyleneglycols; polyglycerols; polyvinylpyrrolidone; polyvinylpyrrolidone co-polymers; carrageenans; or mixtures of these substances.

Disintegrants in solid dosage forms are selected from the group consisting of: starch; modified starches; sodium starch glycolate; methylcellulose; sodium carboxymethylcellulose; 2-hydroxyethylcellulose; 2-hydroxypropylcellulose; polyvinylpyrrolidone; polyvinylpyrrolidone co-polymers; or mixtures of these substances.

Lubricants in solid dosage forms and powders are selected from the group consisting of: metal soaps such as magnesium stearate, calcium stearate, and zinc stearate; stearic acid; talc; silicon dioxide; or mixtures of these substances.

Emollients, as basic excipients in semi-solid and liquid forms of the formulation such as ointments, creams, and lotions, are selected from the group consisting of: paraffin wax; mineral oil; petroleum jelly; ozokerite; yellow or white beeswax; synthetic esters of higher fatty acids like isopropyl myristate, isopropyl palmitate, trimethylolpropane tristearate, glyceryl tricaprylate; synthetic waxes such as lauryl laurate; liquid natural waxes such as jojoba oil; plant oils such as soybean oil, sweet almond oil, sunflower seed oil, fish oil, olive oil, wheat germ oil, corn germ oil, avocado oil, palm oil, cocnut oil; semi-solid or liquid silicones; higher fatty alcohols such as cetyl alcohol, stearyl alcohol, oleyl alcohol; or mixtures of these substances.

In creams, ointments, and other liquid forms of the formulation such as lotions and shampoos, emulsifiers are selected from the group consisting of: metal salts of sulphates of higher fatty alcohols like sodium laurylsulphate, sodium lauryl ethyleneglycolsulphate, sodium lauryl diethyleneglycolsulphate; ethoxylates of higher fatty alcohols such as polyoxyethylene(2) laurylether, polyoxyethylene(10) laurylether, polyoxyethylene(23) laurylether, and others,

where 2, 10 and 23 represent average number of ethyleneglycol units bounded on higher fatty alcohol; ethoxylates of higher fatty acids such as polyoxyethylene(2) laurate, polyoxyethylene(10) laurate, polyoxyethylene(23) laurate, and others, wherein 2, 10 and 23 represent average number of ethyleneglycol units bounded on higher fatty acid; esters of sorbitan such as polyoxyethylene sorbitan monolaurate; lanolin; ethoxylated lanolins; glyceryl monostearate; beeswax ethoxylates; or mixtures of these substances.

Tensides in liquid forms of the formulation like shampoos, and solid forms like soaps, are selected from the group consisting of: metal salts of sulphates of higher fatty alcohols such as sodium laurylsulphate, sodium lauryl ethyleneglycolsulphate, sodium lauryl diethyleneglycolsulphate, potassium laurylsulphate, potassium lauryl ethyleneglycolsulphate, potassium lauryl diethyleneglycolsulphate, ammonium laurylsulphate, ammonium lauryl ethyleneglycolsulphate, ammonium lauryl diethyleneglycolsulphate, sodium or potassium cocoamphodipropionate; disodium or dipotassium cocoamphodiacetate; polyoxyethylene(10) laurylether, polyoxyethylene(23) laurylether, polyoxyethylene(10) stearylether, polyoxyethylene(23) stearylether, polyoxyethylene(10) oleylether, polyoxyethylene(23) oleylether, and other ethoxylates of higher fatty alcohols with H.L.B. value ≥10; polyoxyethylene(10) laurate, polyoxyethylene(23) laurate, polyoxyethylene(10) stearate, polyoxyethylene(23) stearate, polyoxyethylene(10) oleate, polyoxyethylene(23) oleate; or other ethoxylates of higher fatty acids with H.L.B. value ≥10; esters of sorbitan such as polyoxyethylene sorbitan monolaurate, polyoxyethylene sorbitan monostearate, polyoxyethylene sorbitan monooleate, or other sorbitan derivatives with H.L.B. value ≥10; mono- or diethanolamides of higher fatty acids; cocoamidopropyl betaine; glycosides of higher fatty alcohols like cocoglucoside; sodium or potassium di(2-ethylhexyl)sulfosuccinate; disodium or dipotassium 2-ethylhexylsulfosuccinate; cationic tensides such as cetyltrimethylammonium bromide, didecyldimethylammonium chloride, benzalkonium chloride, cetylbenzyldimethylammonium bromide, cetylpyridinium chloride; metal salts of higher fatty acids such as sodium or potassium salts of lauric, myristic, palmitic, stearic, oleic, or ricinoleic acid; or mixtures of these substances.

Humectants are selected from the group consisting of: glycerol; 1,2-propyleneglycol; 1,3-propyleneglycol; hexyleneglycol; 1,3-butanediol; polyethyleneglycols; polyglycerols; sorbitol; xylitol; saccharose; urea; sodium hyaluronate; or mixtures of these substances.

Solvents in liquid forms of the formulation like lotions are selected from the group consisting of: purified water; ethanol; 1-propanol; isopropanol; isosorbide dimethylether; diethyleneglycol monomethylether; diethyleneglycol dimethylether; diethyleneglycol monoethylether; diethyleneglycol diethylether; triethyleneglycol monomethylether; triethyleneglycol dimethylether; triethyleneglycol monoethylether; triethyleneglycol diethylether; ethyl lactate, or other lactate esters with lower aliphatic alcohols; triethylhexanoin; or mixtures of these substances.

Thickeners in the formulation are selected from the group consisting of: polyacrylic acid, its co-polymers, or their sodium, potassium, or triethanolamine salts; methylcellulose; sodium carboxymethylcellulose; 2-hydroxyethylcellulose; 2-hydroxypropylcellulose; starch; modified starches; polyglycerols; polyethyleneglycols; gelatin; pectin; agar agar; carrageenans; gum arabic; alginic acid; sodium alginate; or mixtures of these substances.

Preservatives are selected from the group consisting of: methyl 4-hydroxybenzoate; ethyl 4-hydroxybenzoate; propyl 4-hydroxybenzoate; butyl 4-hydroxybenzoate; triclosan; chlorhexidine or its dihydrochloride, diacetate, or digluconate salts; sorbic acid; potassium sorbate; benzoic acid; sodium benzoate; 2-bromo-2-nitropropane-1,3-diol; 2-hydroxybiphenyl; 2-phenoxyethanol; 4-chloro-m-cresol; thymol; eugenol; or mixtures of these substances.

Antioxidants are selected from the group consisting of: 2,6-di-*terc*-butyl-4-hydroxytoluene (BHT); *terc*-butylhydroxyanisole (BHA); tocoferol; tocoferol acetate; ascorbic acid; ascorbyl palmitate; or mixtures of these substances.

Stabilizers are selected from the group consisting of: disodium ethylenediamine tetraacetate ($Na_2EDTAx2H_2O$); disodium N-(2-hydroxyethyl)ethylenediamine triacetate [$Na_2H(HEDTA)$]; disodium diethylenetriamine pentaacetate [$Na_2H_3(DTPA)$]; disodium citrate [$Na_2(C(OH)(COOH)(CH_2COO)_2$]; or mixtures of these substances.

Pharmaceutical or cosmetic active substances in the formulation are selected from the group known to those skilled in the art as: local antiseptic; anti-fungal agent; anti-inflammatory and/or antiphlogistic agent; vasoprotective; immune stimulant; antioxidant; astringent; anti-acne agent; skin pigment regulation agent; dermatoses treatment agent; and other active

substances which can contribute and/or enhance basic biological actions of silicon which is effectively released from micronized clinoptilolite (**MC**).

Local antiseptic is selected from the group consisting of: ethanol; isopropanol; 1-propanol; benzyl alcohol; 2-phenoxyethanol; 2,4-dichlorobenzyl alcohol; triclosan; 2-phenylphenol; 4-chloro-m-cresol; hexachlorophene; cresol; 2,4,6-tribromo-m-cresol; carvacrol; thymol; phenylmercury(II) acetate; phenylmercury(II) nitrate; chlorhexidine or its dihydrochloride, diacetate, or digluconate salts; hexetidine; chloroxine; 8-hydroxyquinoline; iodochlorohydroxyquinoline; didecyldimethylammonium chloride; benzalkonium chloride; hexadecyltrimethylammonium bromide; cetylpyridinium chloride; gentian violet; methylene blue; acriflavine; briliant green; ethacridine lactate; iodine; povidone-iodine or other iodine inclusion complexes; iodine monochloride; iodoform; sodium iodate; iodic acid; hexamethylenetetramine tetraiodide; hydrogen peroxide; magnesium peroxide; calcium peroxide; zinc peroxide; potassium permanganate; zinc permanganate; urea hydrogen peroxide adduct; silver-proteine; basic aluminum acetates; boric acid; or compatible mixtures of these substances.

Antifungal agent is selected from the group consisting of: clotrimazole; miconazole; fluconazole; ketoconazole; itraconazole; econazole; saperconazole; terconazole; griseofulvin; isoconazole; tolnaftate; terbinafine; undecylenic acid or its salts with pharmaceutically acceptable bases; propionic acid or its salts with pharmaceutically acceptable bases; cyclopyrox; triacetin; salicylanilide; hexetidine; pyrithione; zinc pyrithione; copper(II) pyrithione; potassium iodide; or mixtures of these substances.

Antinflammatory and/or antiphlogistic agent is selected from the group consisting of: paracetamol; metamizol sodium; acetylsalicylic acid and its salts with pharmaceutically acceptable bases; salicylic acid and its salts with pharmaceutically acceptable bases; salsalate; methyl salicylate; ethyl salicylate; benzyl salicylate; 2-hydroxyethyl salicylate; salicylamide; phenylbutazone sodium; propyphenazone; oxyphenbutazone; mofebutazone; bumadizon calcium; phenazone; ethenzamide; ketoprofen, ibuprofen, naproxen, flurbiprofen, pirprofen, mefenamic acid, fluphenamic acid, thiaprofenic acid or their salts with pharmaceutically acceptable bases; diclofenac sodium; indomethacin; piroxicam; meloxicam; codeine; caffeine; extract of St John's wort (*Hypericum perforatum*); azulene; extract of Chamomile (*Matricaria recutita*); extract of Marigold (*Calendula officinalis*); extract of Arnica (*Arnica montana*);

extract of White Willow (*Salix alba*); extract of Spiny Restharrow (*Ononis spinosa*); menthol; essential oil or extract of Mint (*Mentha piperita*); eucalyptol; essential oil or extract of Rosemary (*Rosmarinus officinalis*); essential oil or extract of Lavender (*Lavandula officinalis*); purified turpentine oil; camphor; pinene; bornyl acetate; terpineol; terpenyl acetate; eugenol; essential oil of Lemon (*Citrus limonum*); essential oil of Orange (*Citrus aurantium*); essential oil of Common Juniper (*Juniperus communis*); essential oil of Clove (*Syzygium aromaticum*); extract of Green Tea (*Camellia sinensis*); extract of Rooibos (*Aspalathus linearis*); extract of Nettle (*Urtica dioica*); extract of Horse-Chestnut (*Aesculus hippocastanum*); extract of Mullein (*Verbascum phlomoides*); extract of European Holly (*Ilex aquifolium*); extract of Borage (*Borago officinalis*); extract of Burdock (*Arctium lappa*); extract of Ribwort Plantain (*Plantago lanceolata*); extract of Century Plant (*Agave americana*); extract of Ground Pine (*Lycopodium clavatum*); methyl nicotinate; benzyl nicotinate; glucosamine sulfate; L-histidine; chondroitin sulfate; hyaluronidase; heparin sodium; coumarin; choline and its salts; sulphur; extracts of plants with significant content of silicic acid (H_4SiO_4) such as Field Horsetail (*Equisetum arvense*), Lungwort (*Pulmonaria officinalis*), Common Knotgrass (Polygonum aviculare), Couch Grass (*Agropyron repens*), Common Agrimony (*Agrimonia eupatoria*), Oat (*Avena sativa*); cortisone; hydrocortisone; dexamethasone; betamethasone; alclometasone; fluprednidene; prednisone; prednisolone; triamcinolone; methylprednisolone; paramethasone; clobetasol; diflorasone; fluocinolone; clocortolone; flumetasone; halometasone; fluocortolone; diflucortolone; mono- or diesters of mentioned synthetic steroids at 17- and/or 21-positions, or 16,17-acetonide derivatives such as hydrocortisone acetate, hydrocortisone-17-butyrate, betamethasone-17-valerate, betamethasone-17,21-dipropionate, alclometasone-17,21-dipropionate, triamcinolone-16α,17α-acetonide; or mixtures of these substances.

Vasoprotecive is selected from the group consisting of: rutin; quercetin; extracts of plants with significant quantities of rutin and/or quercetin such as Rue (*Ruta graveolens*), or Cowslip (*Primula officinalis*); troxerutin; epicatechin; epigallocatechin; epigallocatechin gallate; extract of Green Tea (*Camellia sinensis*); diosmin; leukocyanidin; aescin; clobenoside; or mixtures of these substances.

Immune stimulant is selected from the group consisting of: lactoferrin; colostrum; propolis or propolis extracts; acemannan; extract of Aloe (*Aloe barbadensis*); extract of Echinacea (*Echinacea angustifolia*); extract of Ginseng (*Panax ginseng*, *Panax quinquefolium*); lentinan;

extract of Shiitake (*Lentinus edodes*); extract of Milk-vetch (*Astragalus gummifera*; *Astragalus tragacanthus*); extract of Elderberry (*Sambucus nigra*); baicalin or extract of Blue skullcap (*Scutellaria lateriflora*); timopentin; ubenimex; interleukin-2; imiquimod or its salts with pharmaceutically acceptable acids; levamisole; pidotimod; or mixtures of these substances.

Antioxidant is selected from the group consisting of: extract of Green Tea (*Camellia sinensis*); extract of Rooibos (*Aspalathus linearis*); extract of Nettle (*Urtica dioica*); extract of Bilberry (*Vaccinium myrtillus*); extract of Orange (*Citrus aurantium*); silymarin; extract of Milk Thistle (*Silybum marianum*); ascorbic acid, its salts, and esters such as ascorbyl palmitate; tocoferol; tocoferol acetate; niacinamide; rutin; quercetin; extracts of plants with significant content of rutin and/or quercetin; cyanidin; hesperidin; diosmin; lycopene; extracts of plants with significant contents of lycopene; resveratrol; tetrahydrocurcumin; rosmarinic acid; extract of Rosemary (*Rosmarinus officinalis*); hypericin; extract of St John's wort (*Hypericum perforatum*); ellagic acid; chlorogenic acid; 3,4-dihydroxycinnamic acid; oleuropein; extract of Olive leaves (*Olea europea*); extract of Grape seed; pycnogenol; carnosine; α-lipoic acid; glutathione; extracts of plants with significant content of silicic acid (H_4SiO_4) such as Field Horsetail (*Equisetum arvense*), Lungwort (*Pulmonaria officinalis*), Common Knotgrass (*Polygonum aviculare*), Couch Grass (*Agropyron repens*), Common Agrimony (*Agrimonia eupatoria*), Oat (*Avena sativa*), Silverweed (*Potentilla anserina*), Common Bistort (*Polygonum bistorta*), Common Sage (*Salvia officinalis*); or mixtures of these substances.

Astringent is selected from the group consisting of: zinc oxide; zinc stearate; zinc tannate; zinc acetate; zinc sulphate; zinc chloride; iron(III) chloride; aluminum sulphate; potassium aluminum sulphate; aqueous basic aluminum acetate; aluminum acetotartarate; bismuth subnitrate; bismuth subcarbonate; bismuth phosphate; bismuth tannate; calamine; copper(II) sulphate; silver nitrate; silver-proteine; aescin; extract of Horse-Chestnut (*Aesculus hippocastanum*); Balsam of Peru; silica gel; kaolin; talc; titanium dioxide; tannic acid; albumin tannate; methylene ditannate; extracts with significant content of tannins such as extracts of Oak bark (*Cortex Quercus ruber*, *Quercus sessiliflora*), Bearberry leaves (*Arctostaphylos uvae ursi*), Common Agrimony (*Agrimonia eupatoria*), Silverweed (*Potentilla anserina*), Common Bistort (*Polygonum bistrota*), Common Sage (*Salvia officinalis*), etc.; or compatible mixtures of these substances.

Agent for treatment of acne is selected from the group consisting of: benzoyl peroxide; chlorhexidine or its dihydrochloride, digluconate, and diacetate salts; salicylic acid; azelaic acid; resorcinol; resorcinol monoacetate; sulphur; sodium thiosulphate; γ-linolenic acid; plant oils with significant content of γ-linolenic acid such as soybean or fish oil; allantoin; extracts of plants with significant content of allantoin like Comfrey (*Symphytum officinale*) or Lungwort (*Pulmonaria officinalis*); d-panthenol; chlorophyll; or mixtures of these substances.

Skin pigment regulation (depigmenting/pigmenting) agent is selected from the group consisting of: hydroquinone; hydroquinone monobenzylether; arbutin; extracts of plants with significant content of hydroquinone glycosides like Bearberry leaves (*Arctostapylos uvae ursi*); 1,3-dihydroxyacetone; troxsalen; extract of *Psoralea corylifolia* seed; metoxsalen; or mixtures of these substances.

Dermatoses treating agent is selected from the group consisting of: γ-linolenic acid; plant oils with significant content of γ-linolenic acid such as soybean or fish oil; purified naphthalan; ammonium bituminosulfonate; dithranol; menthol; camphor; N-acetylcysteine; allantoin; extracts of plants with significant content of allantoin like Comfrey (*Symphytum officinale*) or Lungwort (*Pulmonaria officinalis*); d-panthenol; chlorophyll; sulphur; sodium thiosulphate; chitin; selenium sulfide; cadmium sulfide; zinc pyrithione; thymol; essential oil of Thyme (*Thymus serpyllum*); essential oil of Clove (*Syzygium aromaticum*); essential oil of Rosemary (*Rosmarinus officinalis*); essential oil of Lavender (*Lavandula officinalis*); or mixtures of these substances.

Beside mentioned, other cosmetic active substances commonly employed for treatment of dry skin, cellulite, wrinkles, mild irritations, and other skin disorders, can be used: vitamins like retinol palmitate, β-carotene, d-panthenol, calcium pantothenate, folic acid, riboflavin, pyridoxine, thiamine; choline chloride; protein hydrolysates; algae extracts; extract of Centaurium (*Erythraea centaurum*); extract of Mullein (*Verbascum phlomoides*); extract of European Holly (*Ilex aquifolium*); extract of Common Ivy (*Hedera helix*); chlorophyll; α-hydroxyacids like glycolic, lactic, malic, citric, and tartaric acid; urea; co-enzyme Q10; or mixtures of these substances.

Preparation of the formulation of the present invention

The formulation of the present invention can be in the form of tablets, capsules, ointments, creams, gels, lotions, shampoos, powders, liquid powders, compact powders, cosmetic masks, suppositories, syrups, suspensions, soaps, and therapeutic patches. The formulation is produced by common procedures known to those skilled in the art of cosmetic and/or pharmaceutical technology [S. C. Gad (Ed.): *Pharmaceutical Manufacturing Handbook: Production and Processes*, Wiley (2008)].

Tablets are produced either by direct compression of homogenized tablet mixture, or by wet granulation of the mixture followed by compression of thus obtained granulate. Micronized clinoptilolite (**MC**) is added during preparation of tablet mixture directly to other excipients: fillers, binders, disintegrants, lubricants, etc.

Capsules are produced by filling of standard, e.g. gelatin, capsules either with micronized clinoptilolite (**MC**), or with homogeneous mixture of **MC** and other excipients.

Ointment is produced by homogenization of micronized clinoptilolite (**MC**) in a melt of one or more liquid (e.g. sweet almond oil), semi-solid (e.g. petroleum jelly), or solid (e.g. beeswax) emollients with optional addition of other functional excipients like fragrances, penetrants, emulsifiers, etc.

Creams are produced by three different method:

(i) by addition of micronized clinoptilolite (**MC**) to already prepared cream;

(ii) by addition of **MC** to the melt of fatty phase, followed by emulsification through slow addition of water phase;

(iii) by addition of **MC** to water phase, followed by emulsification through slow addition of molten fatty phase.

Depending on emulsifiers employed, the obtained cream can be oil-in-water (O-W) emulsion, or water-in-oil (W-O) emulsion.

Lotion is produced by homogenization of micronized clinoptilolite (**MC**) in aqueous-alcoholic solution containing humectants (e.g. glycerol), thickeners (e.g. gum arabic), and optionally other functional excipients such as astringents, fragrances, colors, etc.

Gel is produced by thickening of above-mentioned lotions with suitable thickeners in higher concentrations in order to obtain a semi-solid product. For example, usual concentration of sodium polyacrylate based thickener Carbopol 934P is 1%.

Shampoo is produced by homogenization of micronized clinoptilolite (**MC**) in previously prepared viscous solution of one or more anionic and/or non-ionic tensides and other excipients such as perfumes, colors, preservatives, etc.

Powder is produced by dry homogenization of micronized clinoptilolite (**MC**) with basic powder excipients such as talc, kaolin, calcium carbonate, etc. Prefumes are previously adsorbed on double-weight amount of basic magnesium carbonate. Thus obtained solid material is than easily homogenized with the rest of the powder. Then the powder is subjected to final homogenization eventually with addition of small amounts of lubricant (e.g. zinc stearate).

Compact powder is produced either by homogenization of above-mentioned powders in smaller amount of fatty phase (10-40%). The latter comprising either anhydrous fatty phase or emulsion (creams of both O-W or W-O types). In all other respects, the production of compact powders is the same as productions of powders, creams and ointments.

Syrup is produced by homogenization of micronized clinoptilolite (**MC**) in viscous aqueous solution of saccharose, honey, glucose, fructose, sorbitol, or their mixtures. In the case of the use of artificial sweeteners, aqueous suspension of **MC** is thickened by addition of edible thickeners like gelatin, pectin, starch, modified starches, sodium carboxymethylcellulose, or mixtures of these substances. Sweetener is selected from the group consisting of: sodium saccharin; acesulfame potassium; sucralose; sodium or calcium cyclamate; xylitol; sorbitol; glycyrrhizin; extract of *Liquorice* root; or mixtures of these substances.

Soap is produced by homogenization of micronized clinoptilolite (**MC**) in a molten mixture of one or more anionic and/or non-ionic tensides and other excipients such as humectants, stabilizers, antioxidants, colors, perfumes, etc. Thus obtained molten mixture is then poured into previously prepared moulds.

In all other pharmaceutical and/or cosmetic forms, procedures are well known to those skilled in the art with several possible variations which are essentially under the scope of this invention.

EXAMPLES

General informations

Analyses of clinoptilolites by sorption-desorption of argon according to BET method was conducted on Micrometrics ASAP 2010 instrument. Analyses of particles size was carried out on Zetasizer NanoZS (Malvern instruments) instrument. Quantitative analyses of silicon (Si) by atomic absorption spectroscopy (AAS) were performed on Analyst 600 (Perkin-Elmer) instrument equipped with grafite furnace (GFAA); detection at 251.6 nm; slit 0.2 nm; injection volume 20 μL. The term room temperature means: 20-25 °C.

Example 1

Preparation of pure micronized calcium clinoptilolite (Ca-MC; $CaAl_2Si_7O_{18}$) from natural clinoptilolite (C; mainly $CaAl_2Si_7O_{18}$)

Clinoptilolite (**C**; 1.00 kg; 1.73 mol; $CaAl_2Si_7O_{18}$) was suspended in demineralized water (5000 mL). To obtained suspension, 37% hydrochloric acid (288 mL; 341.28 g of solution; 126.27 g HCl; 3.46 mol; 2 equiv.) was added. Suspension was stirred at room temperature for 1 h. Then, the product was separated by filtration, and washed with demineralized water (3x500 mL). The product was dried under high vacuum at 105 °C during 20 h, yielding 934.51 g (93.5%) of acidic (H^+) form of clinoptilolite (**H-C**; $H_2Al_2Si_7O_{18}$) as white to white off powder.

Thus obtained product (500.00 g; 0.928 mol) was suspended in demineralized water (2000 mL). To this suspension, previously prepared solution of calcium chloride dihydrate ($CaCl_2 \cdot 2H_2O$; 272.81 g; 1.86 mol; 2 ekv.) in demineralized water (1000 mL) was added at once. The suspension was stirred at room temperature during 6 h. Then, the product was filtered, washed with demineralized water (5x500 mL), and dried at 105 °C under high vacuum during 20 h, giving pure calcium clinoptilolite (**Ca-C**; $CaAl_2Si_7O_{18}$) as white off powder.

Analysis for $CaAl_2Si_7O_{18}$; Calculated: CaO 9.69%; Al_2O_3 17.62%; SiO_2 72.69%; Found: CaO 9.41%; Al_2O_3 17.49%; SiO_2 72.29%.

Such prepared pure calcium clinoptilolite was subjected to described micronization process affording micronized clinoptilolite **Ca-MC** of particles size ranging from 100 nm to 2 μm (the peak of Gauss-type curve was around 1 μm), of BET total surface area of 31.8 m^2/g (nitrogen).

Example 2

Preparation of pure micronized magnesium clinoptilolite (Mg-MC; $MgAl_2Si_7O_{18}$) from natural clinoptilolite (C; mainly $CaAl_2Si_7O_{18}$)

Clinoptilolite (**C**; 1.00 kg; 1.73 mol; $CaAl_2Si_7O_{18}$) was suspended in demineralized water (5000 mL). To obtained suspension, 37% hydrochloric acid (288 mL; 341.28 g of solution; 126.27 g HCl; 3.46 mol; 2 equiv.) was added. The suspension was stirred at room temperature for 1 h. Then, the product was separated by filtration, and washed with demineralized water (3x500 mL). The product was dried under high vacuum at 105 °C during 20 h, yielding 934.51 g (93.5%) of acidic (H^+) form of clinoptilolite (**H-C**; $H_2Al_2Si_7O_{18}$) as white to white off powder.

Thus obtained product (500.00 g; 0.928 mol) was suspended in demineralized water (2000 mL), and previously prepared solution of magnesium chloride hexahydrate ($MgCl_2 \cdot 6H_2O$; 282.00 g; 1.39 mol; 1.5 ekv.) in demineralized water (2000 mL) was added. The suspension was stirred at room teemperature for 20 h. Then, the product was separated by filtration, washed with demineralized water (5x500 mL), and dried at 105 °C under high vacuum during

20 h affording pure magnesium clinoptilolite (**Mg-C**; $MgAl_2Si_7O_{18}$) in the form of white off powder.

Analysis for $MgAl_2Si_7O_{18}$; Calculated: MgO 7.16%; Al_2O_3 18.12%; SiO_2 74.72%; Found: MgO 6.97%; Al_2O_3 17.85%; SiO_2 74.13%.

Pure magnesium clinoptilolite was micronized in described microniser giving micronized product **Mg-MC** of particles size 100 nm to 2 μm (the peak of Gauss-type curve was around 1 μm).

Example 3

Preparation of pure micronized zinc clinoptilolite (Zn-MC; $ZnAl_2Si_7O_{18}$) from natural clinoptilolite (C; mainly $CaAl_2Si_7O_{18}$)

Clinoptilolite (**C**; 100.00 g; 0.173 mol; $CaAl_2Si_7O_{18}$) was suspended in demineralized water (500 mL). To thus obtained suspension, 37% hydrochloric acid (30 mL; 35.55 g of solution; 13.15 g HCl; 0.36 mol; 2.1 equiv.) was added drop-wise during 15 minutes. The reaction mixture was stirred at room temperature during 1 h. Then, the crystals were separated by filtration, washed with demineralized water (3x30 mL), and dried at 105 °C under high vacuum during 20 h, yielding 92.71 g (92.7%) of acidic (H^+) form of clinoptilolite (**H-C**; corresponds to $H_2Al_2Si_7O_{18}$) as white off powder.

This product (50.00 g; 0.09 mol) was suspended in demineralized water (200 mL), and previously prepared solution of zinc sulphate heptahydrate ($ZnSO_4 \cdot 7H_2O$; 38.81 g; 0.135 mol; 1.5 equiv.) in demineralized water (200 mL) was added at once. The reaction mixture was stirred at room temperature for 20 h. The product was filtered, washed with demineralized water (5x500 mL), and dried at 105 °C under high vacuum for 20 h, affording pure zinc clinoptilolite (**Zn-C**; $ZnAl_2Si_7O_{18}$) as white off powder.

Analysis for $ZnAl_2Si_7O_{18}$; Calculated: ZnO 13.48%; Al_2O_3 16.88%; SiO_2 69.64%; Found: ZnO 13.32%; Al_2O_3 16.83%; SiO_2 69.65%.

This product was subjected to micronization in described microniser giving zinc clinoptilolite (**Zn-MC**) of enhanced mesoporosity; particles size from 100 nm to 2 μm (the peak of Gauss-type curve was around 1 μm).

Example 4

Study of release of silicon from clinoptilolite

The study of releasing of silicon (Si) from clinoptilolite was performed by stirring the samples (20.00 g) of clinoptilolite (**C**) and micronized clinoptilolite (**MC**) in double distilled water (100 mL) for 1 h. Then, suspended zeolites were removed by filtration and obtained filtrates were diluted to 100 mL with distilled water, and quantitatively analysed by atomic absorption spectroscopy (AAS; see General informations). From thus obtained results, the contents of silicon (Si) as well as corresponding equivalent amounts of silicic acid (calculated as H_4SiO_4) released from 1.00 g of the samples were calculated.

The same experiments were repeated and the triturations were carried out overnight (for 16 hrs).

In all experiments, only high-density polyethylene flasks and equipments were employed in order to exclude traces of silicon which might be released from glassware equipments. Additionaly the content of silicon (Si) in thus double-distilled water was analysed and calculated in this study (through the blank entries).
Results are given in Table 1.

Example 5

Preparation of 250 mg tablets of micronized calcium clinoptilolite (Ca-MC)

Content (100 g of tablet mixture): (a) Microcrystalline cellulose (40.00 g; 40%), (b) lactose monohydrate (28.00 g; 28%), (c) sodium starch glycolate (3.00 g; 3%), (d) polyvinylpyrrolidone (3.00 g; 3%), (e) magnesium stearate (1.00 g; 1%), (f) micronized calcium clinoptilolite (**Ca-MC**; 25.00 g; 25%),

Procedure: Ingredients (a), (b), (c), (d) and (f) were homogenized in dry homogenizer during 15 minutes. Then, (e) was added and homogenization was continued for 15 minutes. Then, homogeneous mixture was milled, and compressed into tablets yielding 100 tablets (1 g); Average tablet weight 993 mg.

Example 6

Preparation of cream with 1% of micronized zinc clinoptilolite (Zn-MC)

Content (100 g of cream): (a) Petroleum jelly (20.00 g; 20%), (b) stearyl alcohol (20.00 g; 20%), (c) lanolin (2.00 g; 2%), (d) isopropyl myristate (1.50 g; 1.5%), (e) sodium laurylsulphate (1.00 g; 1%), (f) methyl 4-hydroxybenzoate (0.20 g; 0.2%), (g) sorbitol (7.00 g; 7%), (h) 1,2-propyleneglycol (3.00 g; 3%), (i) micronized zinc clinoptilolite (**Zn-MC**; 1.00 g; 1%), (j) purified water (44.30 g; 44.3%).

Procedure: (a) and (b) were carefully melted with stirring, and further heated to 80 °C with stirring. Then, (c), (d), (e) and (f) were added. The mixture was stirred at this temperature for 15-20 min. Water phase was prepared by dissolution of (g) and (h) in (j), and added drop-wise during 30 min. Thus obtained emulsion was vigorously stirred at temperatures between 80 °C and 50 °C during 15-20 minutes, and then (i) was added. The cream was vigorously stirred at 50 °C for 20-40 minutes, and then carefully cooled to room temperature with constant stirring. The product was additionally homogenized by mixing at room temperature during 15 min. The product was a white, fine, semi-solid cream with only slight smell of lanoline.

Example 7

Preparation of cream with 10% micronized clinoptilolite and 2% methyl salicylate for treatment of rheumatic disorders

Content (100 g of cream): (a) Petroleum jelly (12.00 g; 12%), (b) glycerol monostearate (4.00 g; 4%), (c) cetyl alcohol (2.00 g; 2%), (d) cetyl palmitate (0.80 g; 0.8%), (e) white beeswax (0.50 g; 0.5%), (f) ceteareth-20 (0.90 g; 0.9%), (g) ceteareth-12 (0.60 g; 0.6%), (h) dimethicone (0.50 g; 0.5 %); (i) sweet almond oil (2.00 g; 2%), (j) jojoba oil (1.00 g; 1%); (k) tocoferol acetate (0.5 g; 0.5%), (l) retinol palmitate (0.05 g; 0.05%), (m) niacinamide (0.20 g;

0.2%), (n) isopropyl myristate (1.20 g; 1.2%); (o) methyl 4-hydroxybenzoate (0.20 g; 0.2%); (p) ethyl 4-hydroxybenzoate (0.03 g; 0.03%); (q) propyl 4-hydroxybenzoate (0.03 g; 0.03%); (r) butyl 4-hydroxybenzoate (0.03g; 0.03%); (s) Carbopol 934P (0.60 g; 0.6%), (t) sodium hydroxide (0.90 g; 20% aqueous solution; 0.9%), (u) 1,2-propyleneglycol (0.50 g; 0.5%), (v) glycerol (2.50 g; 2.5%), (w) micronized clinoptilolite (**MC**; 10.00 g; 10%), (z) mixture of essential oils of Lavender and Lemon (1.00 g; 2:1, w/w; 1%), (x) methyl salicylate (2.00 g); (y) purified water (55.96 g; 55.96%).

Procedure: (a), (b), (c), (d), (e), (f) and (g) were melted by careful heating. Thus obtained melt was heated to 70 °C, and then (h), (i), (j) and (n) were added. To obtained melt (k), (l), (m), (o), (p), (q) and (r) were added, and mixture was stirred at this temperature during 15 minutes. To this mixture, water phase was added drop-wise at 70 °C during 30 minutes. Water phase was previously prepared by dissolution of (s), (u) and (v) in (y). Then, (t) was added to the cream. Obtained emulsion was vigorously stirred at 70 °C to 50 °C during 20-30 minutes. Then (w) was added to the cream. The cream was stirred at 50 °C during 15 minutes, and then cooled to 40 °C. At this point, (z) and (x) were added. The product was homogenized at temperatures between 40 °C and room temperature by vigorous mixing during 30 minutes. The product was in the form of nice, greenish semi-solid cream of pleasant scent.

Example 8

Preparation of ointment with 10% of micronized clinoptilolite (MC)

Content (100 g of ointment): (a) Petroleum jelly (40.00 g; 40%), (b) heavy mineral oil (29.40 g; 29.4%), (c) soyben oil (20.00 g; 20%), (d) micronized clinoptilolite (**MC**; 10.00 g; 10%), (e) d-panthenol (0.50 g; 0.5%), (f) tocoferol acetate (0.10 g; 0.1%).

Procedure: (b) and (c) were slowly heated to 60 °C, and then (a) was added with stirring. The mixture was stirred at this temperature until clear oily liquid was formed. Then (d), (e) and (f) were added, and stirring was continued for 15 minutes. Thus obtained mixture was carefully poured into small (25 mL) plastic jars. The product was in the form of fine, white to slightly greenish, odourless, semi-solid ointment.

Example 9

Preparation of gel with 10% micronized calcium clinoptilolite (Ca-MC)

Content (100 g of gel): (a) 1,2-Propyleneglycol (30.00 g; 30%), (b) polypropyleneglycol 425 (1.50 g; 1.5%), (c) glycerol (2.50 g; 2.5%), (d) Carbopol 934P (1.00 g; 1%), (e) triethanolamine (q.s.), (f) micronized calcium clinoptilolite (**Ca-MC**; 10.00 g; 10%), (g) sodium benzoate (0.20 g; 0.2%), (h) potassium sorbate (0.30 g; 0.30%), (i) anhydrous citric acid (0.50 g; 0.5%), (j) purified water (54.00 g; 54%).

Procedure: To (j) with vigorous stirring (d) was added, and the mixture was stirred at room temperature during 2 h giving clear viscous liquid. Then, (a), (b), (c), (g), (h) and (i) were added, and the mixture was stirred at room temperature for additional 10 min. Then, (f) was added and stirred for 10 minutes, when (e) was added and mixed until white gel was obtained (pH should be between 6-6.5). The product was in the form of fine, white, odourless semi-solid gel.

Example 10

Preparation of cosmetic mask with 20% of micronized clinoptilolite (MC)

Content (100 g of mask): (a) Petroleum jelly (8.50 g; 8.5%), (b) glycerol monostearate (4.00 g; 4%), (c) cetyl alcohol (2.00 g; 2%), (d) cetyl palmitate (0.80 g; 0.8%), (e) beeswax (2.50 g; 2.5%), (f) ceteareth-20 (0.90 g; 0.9%), (g) ceteareth-12 (0.60 g; 0.6%), (h) dimethicone (0.50 g; 0.5%), (i) sweet almond oil (3.00 g; 3%), (j) jojoba oil (1.00 g; 1%), (k) tocoferol acetate (0.50 g; 0.5%), (l) retinol palmitate (0.05 g; 0.05%), (m) nicotinamide (0.20 g; 0.2%), (n) isopropyl myristate (1.20 g; 1.2%), (o) methyl 4-hydroxybenzoate (0.20 g; 0.2%); (p) ethyl 4-hydroxybenzoate (0.03 g; 0.03%), (q) propyl 4-hydroxybenzoate (0.03 g; 0.03%), (r) butyl 4-hydroxybenzoate (0.03 g; 0.03%), (s) Carbopol 934P (0.60 g; 0.6%), (t) sodium hydroxide (0.90 g of 20% aqueous solution), (u) 1,2-propyleneglycol (0.50 g; 0.5%), (v) glycerol (2.50 g; 2.5%), (w) micronized clinoptilolite (**MC**; 20.00 g; 20%), (z) mixture of essential oils of Lavender and Lemon (1.00 g; 2:1, w/w; 1%), (x) purified water (48.46 g; 48.46%).

Procedure: (a), (b), (c), (d), (e), (f) and (g) were carefully melted. Thus obtained melt was further heated to 70-75 °C with constant stirring. Then, (h), (i), (j) and (n) were added,

followed by (k), (l), (m), (o), (p), (q) and (r), and stirring was continued during additional 15 min. To this suspension, aqueous phase was added at 70-75 °C drop-wise during 30 min. The aqueous phase was previously prepared by dissolution of (s), (u) and (v) in (x). Then, (t) was added to the emulsion. The latter was vigorously stirred at 70-50 °C during 20-30 min. Then, (w) was added. The product was vigorously stirred at 50 °C during 30 min, and then was cooled to 40 °C. Then, (z) was added, and stirring was continued to room temperature during 30 minutes. The emulsion was additionally homogenized by mixing at room temperature for 30 min. The product was obtained in the form of fine, greyish-white, semi-solid creamy mask of pleasant scent.

Example 11

Preparation of powder with 10% of micronized clinoptilolite (MC)

Content (100 g of powder): (a) Talc (54.00 g; 54%), (b) kaolin (20.00 g; 20%), (c) micronized clinoptilolite (**MC**; 10.00 g; 10%), (d) precipitated calcium carbonate (5.00 g; 5%), (e) zinc oxide (5.00 g; 5%), (f) zinc stearate (5.00 g; 5%), (g) heavy mineral oil (1.00 g; 1%).

Procedure: In a homogenizer (a), (b) and (c) were added, and the mixture was mixed for 10 minutes. Then (d), (e), (f) and (g) were added, and the resulting mixture was mixed for 30 minutes, giving white, fine gentle powder, without dusting tendencies.

Example 12

Preparation of shampoo with 3% of micronized clinoptilolite (MC) and 1% of ketoconazole

Content (100 g of shampoo): (s) Sodium laurylsulphate (7.00 g; 7%), (b) cocoamidopropyl betaine (2.50 g; 2.5%), (c) cocodiethanolamide (1.50 g; 1.5%), (d) polyoxyethylene(23) laurylether (2.00 g; 2%), (e) polysorbate 20 (2.50 g; 2.5%), (f) disodium laurylsulfosuccinate (5.00 g; 5%), (g) methylcellulose (0.35 g; 0.35%), (h) micronized clinoptilolite (**MC**; 3.00 g; 3%), (i) ketoconazole (1.00 g; 1%), (j) glycerol (4.00 g; 4%), (k) 1,2-propyleneglycol (2.50 g; 2.5%), (l) disodium edetate dihydrate (0.20 g; 0.2%), (m) anhydrous citric acid (0.20 g; 0.2%), (n) sodium benzoate (0.20 g; 0.2%), (o) potassium sorbate (0.30 g; 0.3%), (p) essential

oil of Lemon (1.00 g; 1%), (q) color solution (0.3 mL; 0.2% aqueous solution of tartrazine), (r) purified water (66.45 g; 66.45%).

Procedure: (g) was dissolved in (r) with stirring. To thus obtained viscous solution (a), (b), (c), (d), (e) and (f) were added, and dissolved by stirring at 40-45 °C during 30 minutes. Then (j), (k), (l), (m), (n) and (o) were added and dissolved by mixing at 40-45 °C for 10 minutes. Then (h), (i), (p) and (q) were added, and mixture was homogenized by stirring at these temperatures during 20-30 minutes. Thus prepared viscous suspension was cooled to room temperature. The product was in the form of yellow-colored, unclear, viscous shampoo of pleasant lemon scent.

Example 13

Preparation of antiseptic soap with 10% micronized clinoptilolite (MC)

Content (100 g of soap): (a) Sodium tallowate (20.00 g; 20%), (b) sodium palmitate (20.00 g; 20%), (c) sodium oleate (15.00 g; 15%), (d) disodium edetate dihydrate (0.25 g; 0.25%), (e) stearic acid (2.00 g; 2%), (f) tocoferol acetate (0.10 g; 0.1%), (g) glycerol (5.00 g; 5%), (h) micronized clinoptilolite (**MC**; 10.00 g; 10%), (i) triclosan (1.00 g; 1%), (j) demineralized water (26.65 g; 26.65%).

Procedure: To (j) heated to 70 °C, (d), (a), (b) and (c) were added, and viscous mixture was stirred at this temperature during 20-30 minutes. Then, (e), (f), and (g) were added. The mixture was homogenized at this temperature for 15-20 minutes. Thus obtained melt was poured into moulds (approx. 30 g). Soaps were soldified by cooling to room temperature. The products obtained were in the form of nice greenish antiseptic soap.

CLAIMS

1. The formulation based on micronized clinoptilolite (**MC**) as therapeutic agent providing highly bioavailable silicon, **characterised by** the composition with variable portions of:

   (i) micronized clinoptilolite (**MC**) of general formula:

   $$(Me^{n+})_{x/n}[(AlO_2)_x(SiO_2)_y]\bullet mH_2O \text{ (MC)}$$

   wherein Me= H, Li, Na, K, Mg, Ca, Zn, Ag, Cu, Mn, Fe; whereas ratio of silicon to aluminum, y:x is from 2.6:1 to 5:1; and number of crystalline water, *m* is between 1 and 20; and with the particles size range from 500 nm to 5 μm; and of

   (ii) one or more excipients which yield in desired pharmaceutical form: tablets, capsules, ointments, creams, gels, lotions, shampoos, powders, liquid powders, compact powders, masks, suppositories, syrups, suspensions, soaps, and therapeutic patches; and,

   optionally, of one or more pharmaceutical or cosmetic active substances which contribute and/or enhance basic biological actions of silicic acid.

2. Formulation according to claim 1, **characterized by that** the excipient is selected from the groups consisting of: fillers; binders; disintegrants; lubricants; emollients; emulsifiers; tensides; humectants; solvents; thickeners; preservatives; stabilizers; colors; perfumes; and/or other functional additives which contribute and/or enhance basic biological actions of silicic acid.

3. Formulation according to claims 1 and 2, **characterized by that** other functional additives are pharmaceutical or cosmetic active substances which contribute and/or enhance basic biological actions of silicic acid are selected from the group consisting of: local antiseptic; antifungal agent; antiinflammatory and/or antiphlogistic; vasoprotective; immune stimulant; antioxidant; astringent; anti acnae agent; skin pigmenting regulation agent; dermatoses treating agent; and other cosmetic active agents; or mixtures of these substances.

4. Formulation according to claim 1-3, **characterized by that** the excipient is filler selected from the group consisting of: microcrystalline cellulose; lactose monohydrate; calcium hydrogenphosphate; sorbitol; starch; modified starches; talc; kaolin; bentonite; montmorillonite; precipitated calcium carbonate; basic magnesium carbonate; calcium silicate; aluminum hydroxide; silicon dioxide; or mixtures of these substances.

5. Formulation according to claim 1-3, **characterized by that** the excipient is binder selected from the group consisting of: gelatin; lactose monohydrate; sorbitol; saccharose; xylitol; maltitol; starch; modified starches; methylcellulose; 2-hydroxyethylcellulose; 2-hydroxypropylcellulose; sodium carboxymethylcellulose; polyethyleneglycols; polyglycerols; polyvinylpyrrolidone; polyvinylpyrrolidone co-polymers; carrageenans; or mixtures of these substances.

6. Formulation according to claim 1-3, **characterized by that** the excipient is disintegrant selected from the group consisting of: starch; modified starches; sodium starch glycolate; methylcellulose; sodium carboxymethylcellulose; 2-hydroxyethylcellulose; 2-hydroxypropylcellulose; polyvinylpyrrolidone; polyvinylpyrrolidone co-polymers; or mixtures of these substances.

7. Formulation according to claim 1-3, **characterized by that** the excipient is lubricant selected from the group consisting of: metal soaps such as magnesium stearate, calcium stearate, zinc stearate; stearic acid; talc; silicon dioxide; or mixtures of these substances.

8. Formulation according to claim 1-3, **characterized by that** the excipient is emollient selected from the group consisting of: paraffin wax; mineral oil; petroleum jelly; ozokerite; yellow or white beeswax; synthetic esters of higher fatty acids like isopropyl myristate, isopropyl palmitate, trimethylolpropane tristearate, glyceryl tricaprylate; synthetic waxes such as lauryl laurate; liquid natural waxes such as jojoba oil; plant oils such as soybean oil, sweet almond oil, sunflower seed oil, fish oil, olive oil, wheat germ oil, corn germ oil, avocado oil, palm oil, cocnut oil; semi-solid or liquid silicones; higher fatty alcohols such as cetyl alcohol, stearyl alcohol, oleyl alcohol; or mixtures of these substances.

9. Formulation according to claim 1-3, **characterized by that** the excipient is emulsifier selected from the group consisting of: metal salts of sulphates of higher fatty alcohols like

sodium laurylsulphate, sodium lauryl ethyleneglycolsulphate, sodium lauryl diethyleneglycolsulphate; ethoxylates of higher fatty alcohols such as polyoxyethylene(2) laurylether, polyoxyethylene(10) laurylether, polyoxyethylene(23) laurylether, and others, where 2, 10 and 23 represent average number of ethyleneglycol units bounded on higher fatty alcohol; ethoxylates of higher fatty acids such as polyoxyethylene(2) laurate, polyoxyethylene(10) laurate, polyoxyethylene(23) laurate, and others, wherein 2, 10 and 23 represent average number of ethyleneglycol units bounded on higher fatty acid; esters of sorbitan such as polyoxyethylene sorbitan monolaurate; lanolin; ethoxylated lanolins; glyceryl monostearate; beeswax ethoxylates; or mixtures of these substances.

10. Formulation according to claim 1-3, **characterized by that** the excipient is tenside selected from the group consisting of: metal salts of sulphates of higher fatty alcohols such as sodium laurylsulphate, sodium lauryl ethyleneglycolsulphate, sodium lauryl diethyleneglycolsulphate, potassium laurylsulphate, potassium lauryl ethyleneglycolsulphate, potassium lauryl diethyleneglycolsulphate, ammonium laurylsulphate, ammonium lauryl ethyleneglycolsulphate, ammonium lauryl diethyleneglycolsulphate, sodium or potassium cocoamphodipropionate; disodium or dipotassium cocoamphodiacetate; polyoxyethylene(10) laurylether, polyoxyethylene(23) laurylether, polyoxyethylene(10) stearylether, polyoxyethylene(23) stearylether, polyoxyethylene(10) oleylether, polyoxyethylene(23) oleylether, and other ethoxylates of higher fatty alcohols with H.L.B. value ≥10; polyoxyethylene(10) laurate, polyoxyethylene(23) laurate, polyoxyethylene(10) stearate, polyoxyethylene(23) stearate, polyoxyethylene(10) oleate, polyoxyethylene(23) oleate; or other ethoxylates of higher fatty acids with H.L.B. value ≥10; esters of sorbitan such as polyoxyethylene sorbitan monolaurate, polyoxyethylene sorbitan monostearate, polyoxyethylene sorbitan monooleate, or other sorbitan derivatives with H.L.B. value ≥10; mono- or diethanolamides of higher fatty acids; cocoamidopropyl betaine; glycosides of higher fatty alcohols like cocoglucoside; sodium or potassium di(2-ethylhexyl)sulfosuccinate; disodium or dipotassium 2-ethylhexylsulfosuccinate; cationic tensides such as cetyltrimethylammonium bromide, didecyldimethylammonium chloride, benzalkonium chloride, cetylbenzyldimethylammonium bromide, cetylpyridinium chloride; metal salts of higher fatty acids such as sodium or potassium salts of lauric, myristic, palmitic, stearic, oleic, or ricinoleic acid; or mixtures of these substances.

11. Formulation according to claim 1-3, **characterized by that** the excipient is humectant selected from the group consisting of: glycerol; 1,2-propyleneglycol; 1,3-propyleneglycol; hexyleneglycol; 1,3-butanediol; polyethyleneglycols; polyglycerols; sorbitol; xylitol; saccharose; urea; sodium hyaluronate; or mixtures of these substances.

12. Formulation according to claim 1-3, **characterized by that** the excipient is solvent selected from the group consisting of: purified water; ethanol; 1-propanol; isopropanol; isosorbide dimethylether; diethyleneglycol monomethylether; diethyleneglycol dimethylether; diethyleneglycol monoethylether; diethyleneglycol diethylether; triethyleneglycol monomethylether; triethyleneglycol dimethylether; triethyleneglycol monoethylether; triethyleneglycol diethylether; ethyl lactate, or other lactate esters with lower aliphatic alcohols; triethylhexanoin; or mixtures of these substances.

13. Formulation according to claim 1-3, **characterized by that** the excipient is thickener selected from the group consisting of: polyacrylic acid, its co-polymers, or their sodium, potassium, or triethanolamine salts; methylcellulose; sodium carboxymethylcellulose; 2-hydroxyethylcellulose; 2-hydroxypropylcellulose; starch; modified starches; polyglycerols; polyethyleneglycols; gelatin; pectin; agar agar; carrageenans; gum arabic; alginic acid; sodium alginate; or mixtures of these substances.

14. Formulation according to claims 1-3, **characterized by that** the pharmaceutical or cosmetic active substance which contribute and/or enhance basic biological actions of silicic acid is local antiseptic selected from the group consisting of: ethanol; isopropanol; 1-propanol; benzyl alcohol; 2,4-dichlorobenzyl alcohol; 2-phenoxyethanol; triclosan; 2-phenylphenol; 4-chloro-m-cresol; hexachlorophene; cresol; 2,4,6-tribromo-m-cresol; carvacrol; thymol; phenylmercury(II) acetate; phenylmercury(II) nitrate; chlorhexidine or its dihydrochloride, diacetate, or digluconate salts; hexetidine; chloroxine; 8-hydroxyquinoline; iodochlorohydroxyquinoline; didecyldimethylammonium chloride; benzalkonium chloride; hexadecyltrimethylammonium bromide; cetylpyridinium chloride; gentian violet; methylene blue; acriflavine; briliant green; ethacridine lactate; iodine; povidone-iodine or other iodine inclusion complexes; iodine monochloride; iodoform; sodium iodate; iodic acid; hexamethylenetetramine tetraiodide; hydrogen peroxide; magnesium peroxide; calcium peroxide; zinc peroxide; potassium permanganate; zinc permanganate; urea hydrogen peroxide adduct; silver-proteine; basic aluminum acetates; boric acid; or compatible mixtures of these substances.

15. Formulation according to claims 1-3, **characterized by that** the pharmaceutical or cosmetic active substance which contribute and/or enhance basic biological actions of silicic acid is antifungal agent selected from the group consisting of: clotrimazole; miconazole; fluconazole; ketoconazole; itraconazole; econazole; saperconazole; terconazole; griseofulvin; isoconazole; tolnaftate; terbinafine; undecylenic acid or its salts with pharmaceutically acceptable bases; propionic acid or its salts with pharmaceutically acceptable bases; cyclopyrox; triacetin; salicylanilide; hexetidine; pyrithione; zinc pyrithione; copper(II) pyrithione; potassium iodide; or mixtures of these substances.

16. Formulation according to claims 1-3, **characterized by that** the pharmaceutical or cosmetic active substance which contribute and/or enhance basic biological actions of silicic acid is antiinflammatory and/or antiphlogistic agent selected from the group consisting of: paracetamol; metamizol sodium; acetylsalicylic acid and its salts with pharmaceutically acceptable bases; salicylic acid and its salts with pharmaceutically acceptable bases; salsalate; methyl salicylate; ethyl salicylate; benzyl salicylate; 2-hydroxyethyl salicylate; salicylamide; phenylbutazone sodium; propyphenazone; oxyphenbutazone; mofebutazone; bumadizon calcium; phenazone; ethenzamide; ketoprofen, ibuprofen, naproxen, flurbiprofen, pirprofen, mefenamic acid, fluphenamic acid, thiaprofenic acid or their salts with pharmaceutically acceptable bases; diclofenac sodium; indomethacin; piroxicam; meloxicam; codeine; caffeine; extract of St John's wort (*Hypericum perforatum*); azulene; extract of Chamomile (*Matricaria recutita*); extract of Marigold (*Calendula officinalis*); extract of Arnica (*Arnica montana*); extract of White Willow (*Salix alba*); extract of Spiny Restharrow (*Ononis spinosa*); menthol; essential oil or extract of Mint (*Mentha piperita*); eucalyptol; essential oil or extract of Rosemary (*Rosmarinus officinalis*); essential oil or extract of Lavender (*Lavandula officinalis*); purified turpentine oil; camphor; pinene; bornyl acetate; terpineol; terpenyl acetate; eugenol; essential oil of Lemon (*Citrus limonum*); essential oil of Orange (*Citrus aurantium*); essential oil of Common Juniper (*Juniperus communis*); essential oil of Clove (*Syzygium aromaticum*); extract of Green Tea (*Camellia sinensis*); extract of Rooibos (*Aspalathus linearis*); extract of Nettle (*Urtica dioica*); extract of Horse-Chestnut (*Aesculus hippocastanum*); extract of Mullein (*Verbascum phlomoides*); extract of European Holly (*Ilex aquifolium*); extract of Borage (*Borago officinalis*); extract of Burdock (*Arctium lappa*); extract of Ribwort Plantain (*Plantago lanceolata*); extract of

Century Plant (*Agave americana*); extract of Ground Pine (*Lycopodium clavatum*); methyl nicotinate; benzyl nicotinate; glucosamine sulfate; L-histidine; chondroitin sulfate; hyaluronidase; heparin sodium; coumarin; choline and its salts; sulphur; extracts of plants with significant content of silicic acid (H_4SiO_4) such as Field Horsetail (*Equisetum arvense*), Lungwort (*Pulmonaria officinalis*), Common Knotgrass (Polygonum aviculare), Couch Grass (*Agropyron repens*), Common Agrimony (*Agrimonia eupatoria*), Oat (*Avena sativa*); cortisone; hydrocortisone; dexamethasone; betamethasone; alclometasone; fluprednidene; prednisone; prednisolone; triamcinolone; methylprednisolone; paramethasone; clobetasol; diflorasone; fluocinolone; clocortolone; flumetasone; halometasone; fluocortolone; diflucortolone; mono- or diesters of mentioned synthetic steroids at 17- and/or 21-positions, or 16,17-acetonide derivatives such as hydrocortisone acetate, hydrocortisone-17-butyrate, betamethasone-17-valerate, betamethasone-17,21-dipropionate, alclometasone-17,21-dipropionate, triamcinolone-16α,17α-acetonide; or mixtures of these substances.

17. Formulation according to claims 1-3, **characterized by that** the pharmaceutical or cosmetic active substance which contribute and/or enhance basic biological actions of silicic acid is vasoprotective selected from the group consisting of: rutin; quercetin; extracts of plants with significant qunatities of rutin and/or quercetin such as Rue (*Ruta graveolens*), or Cowslip (*Primula officinalis*); troxerutin; epicatechin; epigallocatechin; epigallocatechin gallate; extract of Green Tea (*Camellia sinensis*); diosmin; leukocyanidin; aescin; clobenoside; or mixtures of these substances.

18. Formulation according to claims 1-3, **characterized by that** the pharmaceutical or cosmetic active substance which contribute and/or enhance basic biological actions of silicic acid is immune stimulant selected from the group consisting of: lactoferrin; colostrum; propolis or propolis extracts; acemannan; extract of Aloe (*Aloe barbadensis*); extract of Echinacea (*Echinacea angustifolia*); extract of Ginseng (*Panax ginseng, Panax quinquefolium*); lentinan; extract of Shiitake (*Lentinus edodes*); extract of Milk-vetch (*Astragalus gummifera*; *Astragalus tragacanthus*); extract of Elderberry (*Sambucus nigra*); baicalin or extract of Blue skullcap (*Scutellaria lateriflora*); timopentin; ubenimex; interleukin-2; imiquimod or its salts with pharmaceutically acceptable acids; levamisole; pidotimod; or mixtures of these substances.

19. Formulation according to claims 1-3, **characterized by that** the pharmaceutical or cosmetic active substance which contribute and/or enhance basic biological actions of silicic acid is antioxidant selected from the group consisting of: extract of Green Tea (*Camellia sinensis*); extract of Rooibos (*Aspalathus linearis*); extract of Nettle (*Urtica dioica*); extract of Bilberry (*Vaccinium myrtillus*); extract of Orange (*Citrus aurantium*); silymarin; extract of Milk Thistle (*Silybum marianum*); ascorbic acid, its salts, and esters such as ascorbyl palmitate; tocoferol; tocoferol acetate; niacinamide; rutin; quercetin; extracts of plants with significant content of rutin and/or quercetin; cyanidin; hesperidin; diosmin; lycopene; extracts of plants with significant contents of lycopene; resveratrol; tetrahydrocurcumin; rosmarinic acid; extract of Rosemary (*Rosmarinus officinalis*); hypericin; extract of St John's wort (*Hypericum perforatum*); ellagic acid; chlorogenic acid; 3,4-dihydroxycinnamic acid; oleuropein; extract of Olive leaves (*Olea europea*); extract of Grape seed; pycnogenol; carnosine; α-lipoic acid; glutathione; extracts of plants with significant content of silicic acid (H_4SiO_4) such as Field Horsetail (*Equisetum arvense*), Lungwort (*Pulmonaria officinalis*), Common Knotgrass (Polygonum aviculare), Couch Grass (*Agropyron repens*), Common Agrimony (*Agrimonia eupatoria*), Oat (*Avena sativa*), Common Agrimony (*Agrimonia eupatoria*), Silverweed (*Potentilla anserina*), Common Bistort (*Polygonum bistorta*), Common Sage (*Salvia officinalis*); or mixtures of these substances.

20. Formulation according to claims 1-3, **characterized by that** the pharmaceutical or cosmetic active substance which contribute and/or enhance basic biological actions of silicic acid is astringent selected from the group consisting of: zinc oxide; zinc stearate; zinc tannate; zinc acetate; zinc sulphate; zinc chloride; iron(III) chloride; aluminum sulphate; potassium aluminum sulphate; aqueous basic aluminum acetate; aluminum acetotartarate; bismuth subnitrate; bismuth subcarbonate; bismuth phosphate; bismuth tannate; calamine; copper(II) sulphate; silver nitrate; silver-proteine; aescin; extract of Horse-Chestnut (*Aesculus hippocastanum*); Balsam of Peru; silica gel; kaolin; talc; titanium dioxide; tannic acid; albumin tannate; methylene ditannate; extracts with significant content of tannins such as extracts of Oak bark (*Cortex Quercus ruber*, *Quercus sessiliflora*), Bearberry leaves (*Arctostaphylos uvae ursi*), Common Agrimony (*Agrimonia eupatoria*), Silverweed (*Potentilla anserina*), Common Bistort (*Polygonum bistrota*), Common Sage (*Salvia officinalis*); or mixtures of these substances.

21. Formulation according to claims 1-3, **characterized by that** the pharmaceutical or cosmetic active substance which contribute and/or enhance basic biological actions of silicic acid is anti acne agent selected from the group consisting of: benzoyl peroxide; chlorhexidine or its dihydrochloride, digluconate, and diacetate salts; salicylic acid; azelaic acid; resorcinol; resorcinol monoacetate; sulphur; sodium thiosulphate; γ-linolenic acid; plant oils with significant content of γ-linolenic acid such as soybean or fish oil; allantoin; extracts of plants with significant content of allantoin like Comfrey (*Symphytum officinale*) or Lungwort (*Pulmonaria officinalis*); d-panthenol; chlorophyll; or mixtures of these substances.

22. Formulation according to claims 1-3, **characterized by that** the pharmaceutical or cosmetic active substance which contribute and/or enhance basic biological actions of silicic acid is skin pigmenting regulation agent selected from the group consisting of: hydroquinone; hydroquinone monobenzylether; arbutin; extracts of plants with significant content of hydroquinone glycosides like Bearberry leaves (*Arctostapylos uvae ursi*); 1,3-dihydroxyacetone; troxsalen; extract of *Psoralea corylifolia* seed; metoxsalen; or mixtures of these substances.

23. Formulation according to claims 1-3, **characterized by that** the pharmaceutical or cosmetic active substance which contribute and/or enhance basic biological actions of silicic acid is dermatoses treating agent selected from the group consisting of: γ-linolenic acid; plant oils with significant content of γ-linolenic acid such as soybean or fish oil; purified naphthalan; ammonium bituminosulfonate; dithranol; menthol; camphor; N-acetylcysteine; allantoin; extracts of plants with significant content of allantoin like Comfrey (*Symphytum officinale*) or Lungwort (*Pulmonaria officinalis*); d-panthenol; chlorophyll; sulphur; sodium thiosulphate; chitin; selenium sulfide; cadmium sulfide; zinc pyrithione; thymol; essential oil of Thyme (*Thymus serpyllum*); essential oil of Clove (*Syzygium aromaticum*); essential oil of Rosemary (*Rosmarinus officinalis*); essential oil of Lavender (*Lavandula officinalis*); or mixtures of these substances.

24. Formulation according to claims 1-3, **characterized by that** the pharmaceutical or cosmetic active substance which contribute and/or enhance basic biological actions of silicic acid is other cosmetic active agent selected from the group consisting of: vitamins like retinol palmitate, β-carotene, d-panthenol, calcium pantothenate, folic acid, riboflavin, pyridoxine, thiamine; protein hydrolysates; algae extracts; extract of

Centaurium (*Erythraea centaurum*); extract of Mullein (*Verbascum phlomoides*); extract of European Holly (*Ilex aquifolium*); extract of Common Ivy (*Hedera helix*); chlorophyll; α-hydroxyacids like glycolic, lactic, malic, citric, and tartaric acid; urea; co-enzyme Q10; or mixtures of these substances.

25. The use of the formulation according to claims 1-24, as therapeutic source of silicon for human or animal organism.

26. The use of the formulation according to claims 1-25, as therapeutic agent for stimulation of immune system.

27. The use of the formulation according to claims 1-25, as antioxidant therapeutic agent for treatment of oxidative stress.

28. The use of the formulation according to claims 1-25, as therapeutic agent for treatment of allergic diseases.

29. The use of the formulation according to claims 1-25, as adjuvant therapeutic agent for treatment of microbial infections.

30. The use of the formulation according to claims 1-25, as therapeutic agent for strengthening of blood vessels walls structure, and for decreasing of their permeability.

31. The use of the formulation according to claims 1-25, as therapeutic agent for stimulation of joints and ligaments functions.

32. The use of the formulation according to claims 1-25, as therapeutic agent for stimulation of osteoblasts and bones mineralization.

33. The use of the formulation according to claims 1-25, as therapeutic agent for prevention of osteoporosis.

34. The use of the formulation according to claims 1-25, as therapeutic agent for decreasing of aluminum resorption from gastrointestinal tract, and thus prevention of neurodegenerative diseases connected with increased aluminum resorption.

35. The use of the formulation according to claims 1-25, as therapeutic agent for improvement of cartilage structure.

36. The use of the formulation according to claims 1-25, as antiinflammatory agent for treatment of acute and chronic inflammatory diseases.

37. The use of the formulation according to claims 1-25, as therapeutic agent for treatment of dermatoses such as: skin irritations; ekzema; seborrheic dermatitis; neurodermitis; atopic dermatitis; and psoriasis.

38. The use of the formulation according to claims 1-25, as therapeutic agent for treatment of dandruff.

39. The use of the formulation according to claims 1-25, as therapeutic agent for treatment of decubitus condition.

40. The use of the formulation according to claims 1-25, as therapeutic agent for treatment of burns.

41. The use of the formulation according to claims 1-25, as therapeutic agent for treatment of wounds.

42. The use of the formulation according to claims 1-25, as therapeutic agent for stimulation of collagen biosynthesis.

43. The use of the formulation according to claims 1-25, as therapeutic agent for stimulation of elastin biosynthesis.

44. The use of the formulation according to claims 1-25, as therapeutic agent for slowing down of skin aging process.

45. The use of the formulation according to claims 1-25, as therapeutic agent for prevention of wrinkles development.

46. The use of the formulation according to claims 1-25, as therapeutic agent for reduction of wrinkles.

47. The use of the formulation according to claims 1-25, as therapeutic agent for stimulation of hair growth.

48. The use of the formulation according to claims 1-25, as therapeutic agent for increasing of hair strength and brightness.

49. The use of the formulation according to claims 1-25, as therapeutic agent for stimulation of nails growth.

50. The use of the formulation according to claims 1-25, as therapeutic agent for stimulation of nails strength.

INTERNATIONAL SEARCH REPORT

International application No
PCT/HR2008/000030

A. CLASSIFICATION OF SUBJECT MATTER
INV. C01B33/00 A61K33/00 A61K8/25 A61K8/26 A61K9/14
A61K31/695 A61Q19/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
C01B A61K A61Q

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	EP 0 522 196 A (CHEVRON RES & TECH [US] CHEVRON USA INC [US]) 13 January 1993 (1993-01-13) claim 1	1-50
A	WO 02/100420 A (UNI DEGLI STUDI DI NAPOLI FEDE [IT]; UNIV PAVIA [IT]; DE GENNARO MAURI) 19 December 2002 (2002-12-19) claims 1,2,10,12-16	1-50
A	DE 10 2007 030198 A1 (NANO GMBH [DE]) 24 January 2008 (2008-01-24) paragraphs [0002], [0008]	1-50
A	US 2004/170694 A1 (COLIC MIROSLAV [US]) 2 September 2004 (2004-09-02) paragraphs [0009] - [0011], [0020], [0021], [0075], [0083]; claims 1,7	1-50

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[X] Further documents are listed in the continuation of Box C.

[X] See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
5 February 2009	13/02/2009

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INTERNATIONAL SEARCH REPORT

International application No
PCT/HR2008/000030

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	EP 1 557 159 A (SHISEIDO CO LTD [JP]) 27 July 2005 (2005-07-27) paragraph [0252]; claim 1	29
A	& RODRIGUEZ-FUENTES G ET AL: "Enterex: Anti-diarrheic drug based on purified natural clinoptilolite" ZEOLITES, ELSEVIER SCIENCE PUBLISHING, US, vol. 19, no. 5-6, 12 November 1997 (1997-11-12), pages 441-448, XP004100793 ISSN: 0144-2449 the whole document	1-50

INTERNATIONAL SEARCH REPORT

Information on patent family members

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US 2004170694 A1	02-09-2004	NONE	
EP 1557159 A	27-07-2005	WO 2004037220 A1	06-05-2004
		KR 20050059177 A	17-06-2005
		US 2006099161 A1	11-05-2006