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Señor
SUPERINTENDENTE DE INDUSTRIA Y COMERCIO
DIVISION DE NUEVAS CREACIONES
E. S. D.

Re: P1.-**UNILEVER N.V.**- Solicitud de patente de Invención en Fase Nacional PCT para **"EMULSION AGUA EN ACEITE QUE COMPRENDE ESTEROLESTERES"**- Clase **A23L 1/30.-** Expediente No. **05-040.025**.-

1. Me refiero a mi memorial de 10 de Enero de 2006.

2. Por medio del presente atentamente ruego a usted, se sirva pronunciarse en relación con la solicitud arriba nombrada, ya que desde el **31 de Agosto de 2005**, esto hace ya casi dos **(2) años**, que fue publicado el extracto de la presente solicitud en la Gaceta de la Propiedad Industrial No. 555 y el examen de patentabilidad correspondiente fue solicitado en su debido momento mediante memorial de 10 de Enero de 2006, sin que haya sido adelantado ningún otro trámite.

3. Cabe anotar que esta demora en el trámite acarrea grave perjuicio para mi representado.

Señor Superintendente,

ALICIA LLOREDA RICAURTE
T.P. 53.215

NRB/fegv

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Industria y Comercio
SUPERINTENDENCIA

DIVISION DE NUEVAS CREACIONES

RADICACIÓN EXPEDIENTE No 05-40025

EL EXTRACTO DE LA PRESENTE SOLICITUD DE **PATENTE DE INVENCION**

FUE PUBLICADO EN LA GACETA DE PROPIEDAD INDUSTRIAL No **555** DE

FECHA **31** DE **AGOSTO** DEL **2005**, EL TERMINO HABIL SEÑALADO POR LA

LEY EXPIRA EL **28** DE **NOVIEMBRE** DEL **2005**

NOTA: Dentro del plazo de los seis (6) meses siguientes a partir de la fecha de publicación en la gaceta de Propiedad Industrial, deberá solicitar y cancelar el examen de patentabilidad so pena de que la solicitud caiga en abandono, de acuerdo con lo establecido en el Artículo 44 de la Decisión 486/2000.

SE PRESENTARON OPOSICIONES POR PARTE DE TERCEROS.

SI _ ___ NO__ _ **X** _ ___

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(54) **CHOLESTEROL LOWERING SUPPLEMENT**

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(57) **ABSTRACT**

The invention provides a composition and a method for lowering blood serum cholesterol levels or for preventing elevated blood serum cholesterol levels, as well as suitable composition comprising (a) one or more phytosterols and/or phytostanols or a mixture thereof capable of reducing cholesterol absorption in the intestine, (b) a composition capable of inhibiting cholesterol biosynthesis, and (c) a composition capable of increasing cholesterol metabolism, wherein at least one of compositions b. and c. is preferably derived from plants.

CHOLESTEROL LOWERING SUPPLEMENT

BACKGROUND OF THE INVENTION

[0001] Cardiovascular diseases (CVD) are the major cause of death and disability in the United States and other industrialized countries despite recent declines in CVD mortality rates, They account for more deaths annually than any other disease, including all forms of cancer combined[i]. In the USA more than 1 million heart attacks occur each year and more than half a million people still die as a result. This enormous toll has focused attention on the possible prevention of CVD by various means, especially through lowering of plasma cholesterol levels. It is well established now that elevated total cholesterol, and in particular low-density lipoprotein (LDL) cholesterol, in plasma plays an important role in the development of atherosclerosis[ii]. Clinical trials have demonstrated clearly that decreasing cholesterol concentrations in plasma can contribute to primary and secondary prevention of coronary events and mortality.[iii] Some studies have estimated a 2% reduction in risk of a coronary artery event by a 1% reduction of total serum cholesterol.[iv]

[0002] Serum cholesterol levels can for example be lowered by a daily intake of some components similar to cholesterol. The components similar to cholesterol reduce the absorption of cholesterol from the intestines into the bloodstream.

[0003] U.S. Pat. No. 5,958,913 discloses a substance comprising a sawed sterol fatty acid ester capable of lowering LDL cholesterol levels in serum and which is fat soluble. The substance can be taken orally as a food additive, food substitute or supplement A daily consumption of saturated sterol fatty acid ester in an mount between about 0.2 and about 20 g/day has been shown to reduce the absorption of endogenic cholesterol.

[0004] Alternatively, compositions that inhibit the cholesterol biosynthesis, for example by inhibiting enzyme 3-hydroxy-3-methylglutaryl coenzyme A reductase (HMG-CoA reductase), an enzyme involved in the cholesterol biosynthesis, can lower blood serum cholesterol by slowing down the production of cholesterol. It is believed that inhibition of HIMG-CoA reductase results in a reduction in hepatic cholesterol synthesis and intracellular cholesterol stores, a compensatory increase in low-density lipoprotein (LDL) receptors, and a subsequent enhanced removal of LDL-cholesterol from plasma. Potent inhibitors of HMG-CoA reductase include for example the compounds referred to as statins, which family comprises for example lovastatin, pravastatin and fluvastatin.

[0005] Several studies suggested a HMG-CoA reductase inhibiting effect of plant extracts. Wang et al.[v] demonstrated HMG-CoA reductase inhibition by several aqueous plant extracts in isolated rat hepatic microsomal preparations. In vivo studies on rats demonstrated the inhibitory effect of traditional Chinese herbs on the cholesterol biosynthesis[vi].

[0006] An enzyme involved in the cholesterol metabolism (conversion of cholesterol into other components) is cholesterol 7α-hydroxylase. Hepatic cholesterol 7α-hydroxylase catalyses the conversion of cholesterol into 7α cholesterol, which is believed to be the rate limiting step in conversion of cholesterol into bile acids. It has been suggested that the increase of cholesterol 7α-hydroxylase activity results in the decrease of blood serum cholesterol and thus is an important pathway of elimination of cholesterol from the body. Methods for treatment of blood serum cholesterol related disorders by inhibition of cholesterol 7α hydroxylase are known in the art.

[0007] WO 91/15213 discloses a method for treatment of cholesterol gallstones employing side-chain hydroxylated cholesterol derivative. In particular the method for treatment of cholesterol gallstones involves ale administration of 25- or 26-hydroxycholesterol, which enhance the activity of cholesterol 7α-hydroxylase, thereby inhibiting for example cholesterol precipitation. Additionally, Wang et al.[vi] showed that several herbal preparations are capable of increasing cholesterol 7α hydroxylase activity.

[0008] According to Raicht et al.[vii], feeding cholesterol to rats increased cholesterol absorption from 1.2 to 70 mg/day and inhibited its synthesis in the liver and enhanced conversion of cholesterol to bile acids from 13.7 to 27.3 mg/day. Furthermore, when given cholesterol to the rats, HMG-CoA reductase activity was inhibited 80%. With beta-sitosterol, cholesterol absorption was inhibited but cholesterol synthesis was increased from 20.0 to 28.8 mg/day.

[0009] The majority of cholesterol lowering compositions currently known in the art include ingredients which either lower cholesterol absorption within the intestines or inhibit cholesterol biosynthesis, e.g., by inhibition of HMG-CoA reductase. As Raicht et al.[vii] demonstrated, the inhibition of cholesterol absorption in the intestine (using β-sitosterol) lowers cholesterol absorption, however, the inhibition of cholesterol absorption in the intestines is followed by an increase in HMG-CoA reductase activity. Increase of the HMG-CoA reductase activity is likely to increase cholesterol biosynthesis and thereby reduce the net effect of cholesterol absorption inhibitors. It is therefore desirable to decrease serum cholesterol levels using combination compositions, which reduce cholesterol absorption within the intestine and additionally inhibit cholesterol biosynthesis, e.g. by inhibiting HMG-CoA reductase activity,

[0010] Methods of reducing plasma cholesterol levels comprising administering a combination of an effective amount of cholesterol biosynthesis inhibitor and an effective amount of cholesterol absorption inhibitor are disclosed in U.S. Pat. No. 5,661,145. The administered combination includes a beta-lactam cholesterol absorption inhibitor and a HMG-CoA reductase inhibitor, which can for example be a statin, for example lovastatin or pravastatin. Other pharmaceutical combination compositions including certain cholesterol absorption inhibitors and cholesterol synthesis inhibitors useful for the treatment of hypercholesterolemia and atherosclerosis are described in U.S. Pat. No. 5,807,834.

[0011] WO 98/01759 describes a method of determining in animal the ratio of serum campesterol to the level of β-sitosterol comprising several steps. Additionally, a combination composition for enhancing in an animal the inhibitory effect of phytostrols on cholesterol enterocyte absorption, which comprises one or more phytosterols which inhibit predominantly one or both of cholesterol and beta sitosterol and one or more compounds which limit cholesterol synthesis, e.g. compounds selected form HMG CoA reductase inhibitors, for example lovostatin, is described. Further described is the main disadvantage of the above composition i.e. the use of statins, and the critical side effects related with the use of statins.

[0012] WO 00/15201 discloses a composition for preventing and treating CVD containing phytosterols or phytostanols as agents inhibiting cholesterol absorption and tocotrienols as agents suppressing cholesterol biosynthesis.

[0013] WO 00/38725 provides combinations of cardiovascular therapeutic compounds for the prophylaxis or treatment of cardiovascular disease including hypercliolesterolemia and atherosclerosis. Combinations disclosed include an ileal bile acid transport inhibitor combined with a cholesteryl ester transport protein inhibitor, a fibric acid derivative, a nicotinic acid derivative, a microsomal triglyceride transfer protein inhibitor, a cholesterol absorption antagonist, or others. Further combinations include a CETP inhibitor with a fibric acid derivative, a nicotinic acid derivative, a bile acid sequestrant, a microsomal triglyceride transfer protein inhibitor, a cholesterol absorption antagonist, or others.

[0014] U.S. Pat. No. 5,958,417 describes a herbal combination comprising Crataegus, Ho Shou Wu, Cassia Seed, Chrysanthemum, Lotus Leaf, Alisma, Hu-Zhang, and Rhubarb wherein the herbs are present in specific weight percentages. However, the herbal combination lacks a potent cholesterol absorption-inhibiting component, such as an effective amount of phytosterol and/or phytostanol.

[0015] Notwithstanding these disclosures, there remains a need in the art for compositions for use in reduction of blood serum cholesterol levels or prevention of elevated blood serum cholesterol levels. Combination compositions including cholesterol absorption inhibitors and cholesterol synthesis inhibitors useful for reduction of blood serum cholesterol levels known in the art are mostly chemically manufactured compositions and the known compositions are therefore undesirable for many people, not natural and costly.

[0016] Additionally, the combination compositions known in the art cannot be used frequently for a longer period since negative side effects will occur. Recent studies have indicated that drugs like statins, often used as HMG-CoA reductase inhibitors in combination compositions, and fibrates can be carcinogenic or cause other undesirable side effects. Newman et al[viii] reported that all members of the classes stains and fibrates cause cancer in rodents. Furthermore, two hyperlipidemic patients treated with simvastatin, a potent inhibitor of HMG-CoA reductase, experienced cheilitis after beginning treatment The rash resolved after discontinuation of medication and subsequent treatment with topical moisturizers and topical corticosteroids (Mebregan et al.[ix]). Khosla et al[x] alerts clinicians to the possible adverse effect of simvastati s and other statins by reporting a case of a 79-year-old man who had onset of fatigue, myalgia, and pleuritic chest pain 3 months after initiation of therapy with simvastatin. Lovastatin was reported to cause liver failure (Tolman[xi]).

[0017] Furthermore, combination compositions known in the art to date only comprise effective amounts of at most two of the blood serum cholesterol reducing activities, selected from reduction of cholesterol absorption in the intestine, inhibition cholesterol of biosynthesis and increase of cholesterol metabolism.

SUMMARY OF THE INVENTION

[0018] The invention disclosed here takes away the above problems and provides combination compositions for use in reduction of blood serum cholesterol levels or prevention of elevated blood serum cholesterol levels comprising one or more phytosterols and/or phytostanols or mixtures thereof capable of reducing cholesterol absorption in the intestine, an effective amount of a plant derived composition capable of Inhibiting cholesterol biosynthesis and an effective amount of a plant derived composition capable of increasing cholesterol metabolism.

[0019] The combination composition disclosed here fulfills the need for cholesterol-reducing combinations having plant-derived active components. The composition according to the invention can therefore be administered for a longer period, thus making it suitable for use in compositions for reduction of blood serum cholesterol levels or prevention of elevated blood serum cholesterol levels. The invention provides a balanced composition for use in reducing blood serum cholesterol levels or preventing elevated blood cholesterol levels. These combination compositions avoid the potential side effects or compensator effects associated with the administration of relatively high levels of components solely directed at reducing cholesterol absorption in the intestine or at inhibiting cholesterol synthesis or at increasing cholesterol metabolism or at only two of those three mechanisms.

[0020] The present invention provides a composition for use in reduction of blood serum cholesterol levels or prevention of elevated blood serum cholesterol levels comprising:

[0021] a. one or more phytosterols and/or phytostanols or mixtures thereof capable of reducing cholesterol absorption in the intestine

[0022] b. an effective mount of a composition capable of inhibiting cholesterol biosynthesis

[0023] c. an effective amount of a composition capable of increasing cholesterol metabolism.

[0024] Advantageously, at least one of compositions b. and c. is derived from plants, i.e. obtained by extraction of plants, Preferably, both composition b. and composition c. are derived from plants, most preferably from different plants or different combinations of plants.

[0025] A further object of the present invention is to provide a method of reducing serum cholesterol levels or preventing elevated blood serum cholesterol levels comprising, administrating to a person a composition comprising one or more phytosterols and/or phytostanols or mixtures thereof capable of reducing cholesterol absorption in the intestine, an effective amount of a plant derived composition capable of inhibiting cholesterol biosynthesis and an effective amount of a plant derived composition capable of increasing cholesterol metabolism.

DESCRIPTION OF THE INVENTION

[0026] The term cholesterol biosynthesis is well known to those skilled in tic art and generally refers to the biochemical pathways of cholesterol synthesis within the animal (e.g. human) body. The term cholesterol metabolism is also well known to those skilled in the art and generally refers to the biochemical pathways involved in the removal of cholesterol from he body.

[0027] The phytosterol and/or phytostanol or mixtures thereof capable of reducing cholesterol absorption in the intestine can be any composition of phytosterol and/or phytostanol or mixtures thereof known in the art and having a cholesterol absorption reducing effect, Phytosterols are steroids derived from plants, yeasts or fungi, which have a hydroxyl group at C-3 and no other functional groups and differ from animal sterols, in particular cholesterol, in that the side chain at position 17 contains a double bond and/or an additional methyl, ethyl or ethylidene group, in particular at position 24. The term phytosterol and/or phytostanol according to the invention, comprises all such analogues, which may further have a double bond at the 5-position in the cyclic unit as in most natural phytosterols, or one or more double bonds at other positions (e.g. 6, 7, 8(9), 8(14), 14, 5/7, or no double bonds in the cyclic unit as in the stanols, or even additiornl methyl groups as e.g. in α_1-sitosterol; the term includes natural phytosterols and derivatives thereof.

[0028] According to a preferred embodiment the phytosterol and/or phytostnols or us thereof are obtained from vegetable oil or wood pulp. More in particular, α-, β-, γ-sitostwol, stigmasterol, ergosterol, campesterol, avenasterol, brassicasterol, desmosterol, chalinosterol, poriferasterol, clionasterol, sitostanol, stigmastanol, campestol or a mixture of one or more of the above phytosterols or phytostanols is used. According to an even more preferred embodiment, sitosterol or mixtures including a sitosterol are used, The concentration of phytosterols andor phytostanols in composition a. is at least 10%, preferably at least 25%, more preferably at least 50%, most preferably at least 80% by dry weight of composition a.

[0029] The plant derived composition capable of inhibiting cholesterol biosynthesis according to the invention preferably comprises a composition capable of inhibiting the enzyme 3-hydroxy-3-methylglutaryl coenzyme A reductase (HMG-CoA reduase inhibitor) and/or inhibiting squalene synthase (squalene synthase inhibitor), HMG-CoA reductase inhibitors can decrease the activity of HMG-CoA reductase, thus inhibiting the conversion of HMG-CoA to mevalonate. The HMG-CoA reductase inhibitors can act on the HMG-CoA reductase directly or indirectly by decreasing the activity of one or more enzymes (e.g. HMG-CoA reductase phosphatse) or cofactors involved in the activation of HMG-CoA reductase or increasing the activity of one or more enzymes (e.g. HMG-CoA reductase kinase) or cofactors involved in the down regulation of HMG-CoA reductase or by decreasing the of HMG-CoA redactase genc transcription or of HMG-CoA reductase RNA translation.

[0030] Squalene synthase inhibitors can decrease the activity of squalene synthase, thus inhibiting the conversion of farnesyl pyrophosphate into squalene. Squalene synthase inhibitors can act on the squalene synthase directly, or indirectly by decreasing the activity of one or more enzymes or cofactors involved in the activation of squalene synthase; or increasing the activity of one or more enzymes or cofactors involved in the down regulation of squalene synthase; or decreasing the squalene synthase gene transcription or squalene synthase RNA translation. According to a preferred embodiment the composition capable of inhibiting cholesterol biosynthesis comprises one or more HMG-CoA reductase inhibitors.

[0031] The composition capable of inhibiting cholesterol biosynthesis is preferably obtained from whole plants or from one or more parts thereof, for example stems, stalks, roots, shoots, rhizomes, tubers, fruits, foliage, kernels, husks, hulls or mixtures thereof, Preferably, the composition is an extract from whole plants or plat parts. Such extracts can be obtained by harvesting the plants, optionally comminuting the plants and/or separating certain parts of the plants, drying, extracting the plats or plant parts using liquid extraction, and optionally concentrating the extract. Drying of the plants is usually necessary to avoid degradation of labile components or microbial contamination upon storage, transport or processing, and results in lowering the water content from e.g. 50-90% to e.g. less than 25%., preferably less than 20%, most preferably between 5 and 15%. Drying is performed under mild conditions i.e. at temperatures between 0 and 80° C., in particular between 10 and 60° C., or by freeze-drying. Before or after drying, the plants or plant parts may be reduced in particle size to coarse fragments or even to fine powder by processes such as grinding, flaking or mincing. Grinding using a hammer mill or equivalent machine is preferred. Extraction according to the invention refers to separating the desired plant material by physical or chemical means, preferably with the aid of a solvent. Suitable solvents include water, water-alcohol mixtures, alcohols, ethers, hydrocarbons or other organic solvents or mixtures thereof Water and water-based solvent mixtures are preferred. Extraction can be performed by maceration, i.e. soaking for a time between e.g. one minute and several hours, optionally using agitation, followed by filtration. For larger scale operations, counter-current extraction can be used. The resulting solutions can be concentrated to liquid or solid extracts using e.g. tin layer evaporators, freeze-drying or spray-drying techniques. Spray-drying resulting in concentrated to dry powders is preferred. Suitable plant extracts containing inhibitors of cholesterol biosynthesis are commercially available.

[0032] Preferred sources for the composition capable of hinibitig cholesterol biosynthesis include *Alisma orientale* (pharmaceutical name Rhizoma alismatis); Typha spp., for example *Typha angustifolia* or *Typha orientalis* (pharmaceutical name Pollen Typhea); *Salvia miltiorhiza* (pharmaceutical name Radix salviae mniltiorrhizae); *Polygonum mulliflorum* (pharmaceutical name Radix Polygoni multiflora); Curcuma spp., for example *C. kwangsiensis, C. longa, C. phaecaulis, C. wenyuin* or *C. aromatica*, (pharmaceutical name Radix curcmae or Rhizoma curcumae); Ligusticum spp., for example *L. wallichii*, (pharmaceutical name Rhizoma Ligustici); Polygonatum spp., for example *P. kingianum, P. sibiricum* or *P. cyrtonema* (pharmaceutical name Rhizoma polygonati); *Polygonum cuspidatum* (pharmaceutical name Rhizoma polygoni cuspidati); Corydalis spp, (pharmaceutical name Rhizoma Corydalis); *Chrysanthemum morifolium* (pharmaceutical name Flos Chrysathemi); *Arthemisia capillaris* (pharmaceutical name Herba Arimisiae capillaris); *Crataegus pinnatifida* or its variations or subspecies pharmaceutical name Fructus Crataegi pinnatifidae); *Eleutheroccus senticocus* (pharmaceutical name Radix eleutherococci senticosi); *Astragalus membranaceus* (pharmaceutical name Radix Astragali). According to a particularly preferred embodiment *Polygonum multiflorum* is used as a source for tile composition capable of inhibiting cholesterol biosynthesis, more preferably at aqueous extract of *Polygonum multiflorum*.

[0033] Preferably, the composition capable of increasing cholesterol metabolism increases the conversion of choles-

terol into bile acids and/or inhibits the esterification of cholesterol. According to an even more preferred embodiment, the composition capable of increasing cholesterol metabolism enhances the activity of cholesterol 7α-hydroxylase (cholesterol-7α hydroxylase activator) and/or inhibits the activity of Acyl-CoA acyl transferase (Acyl-CoA acyl transferase inhibitor).

[0034] A cholesterol 7α-hydroxylase activator can enhance the activity of cholesterol 7α-hydroxylase, thus enhance the conversion of cholesterol into 7α-cholesterol. Cholesterol 7α-hydroxylase activators can act on the cholesterol 7α-hydroxylase directly or indirectly by increasing the activity of enzymes and cofactors involved in the activation of cholesterol 7α-hydroxylase or decrease the activity of enzymes or cofactors involved in the down-regulation of cholesterol 7α-hydroxylase (e.g. by effecting enzymes involved in the phosphorylation and dephosphorylation of cholesterol 7α-hydroxylase) or increasing the cholesterol 7α-hydroxylase gene transcription or cholesterol 7α hydroxylase RNA translation.

[0035] Acyl-CoA acyl transferase inhibitors can inhibit the conversion of cholesterol into cholesteryl oleate. Acyl-CoA acyl transferase inhibitors can act on tile Acyl-CoA acyl transferase directly, or indirectly by decreasing the activity of one or more enzymes or cofictors involved in the activation of Acyl-CoA acyl transferase or increasing the activity of one or more enzymes or cofactors involved in the down regulation of Acyl-CoA acyl transferase or decreasing the Acyl-CoA acyl transferase gene transcription or Acyl-CoA acyl tslerase RNA translation. According to a preferred embodiment, the composition capable of increasing cholesterol metabolism comprises one or more cholesterol 7a-hydroxylase activators, which act systemically.

[0036] The composition capable of enhancing cholesterol metabolism is preferably obtained from whole plants or from one or more parts thereof, for example stems, stalks, roots, shoots, rhizomes, tubers, fruits, foliage, kernels, husks, hulls or mixtures thereof. The whole plants or plant parts providing enhancers of cholesterol metabolism may be subjected to extraction as described above for plants providing inhibitors of cholesterol biosynthesis, Suitable extracts containing the plant-derived metabolic enhancers are commercially available.

[0037] Preferred sources for obtaining the compositions capable of increasing cholesterol metabolism include *Polygonum multiflorum* (pharmaceutical name Radix Polygoni multiflora); Curcuma spp., for example *C. kwangsiensis, C. longa, C. phaecaulis, C. wenyuin* or *C. aromatica*, pharmaceutical name Radix curcumae or Rhizoma curcumae); Ligusticum spp., for example *L. wallichii*, (pharmaceutical name Rhizoma Ligustici); Polygonatum spp., for example *P. kingianum, P. sibiricum* or *P. cyrtonema* (pharmaceutical name Rhizoma polygonati); *Polygonum cuspidatum* (pharmaceutical name Rhizoma polygoni cuspidati); Corydalis spp. (pharmaceutical name Rhizoma Corydalis); *Chrysanthemum morifolium* (pharmaceutical name Flos Chrysanthemi); *Arthemisia capillaris* (pharmaceutical name Herba Artimisiae capillaris); *Acanthopanax senticosus* (pharmaceutical name Radix Astragali). According to a particularly preferred embodiment *Chrysanthemum morfolium* is used as a source for the composition capable of increasing cholesterol metabolism, more preferably an aqueous extract *Chrysanthemum morifolium.*

[0038] The dry weight ratio between composition a. and the combination of compositions b. and c. is preferably between 0:1 and 1:10, more preferably between 4:1 and 1:4. The dry weight ratio between compositions b. and c, is preferably between 10:1 and 1:10, more preferably between 3:1 and 1:3.

[0039] Elevated serum cholesterol levels are often closely related to a reduced vascular health. It is therefore advantageously to include in the composition for use in reduction of blood serum cholesterol levels or prevention of elevated blood serum cholesterol levels, an effective amount of a composition for the prevention and/or treatment of vascular disorders. Preferably one or more compounds selected from the group of polyunsaturated fatty acids, antioxidants, phospholipids, folic acid, vitamin B12, vitamin B6, magnesium, coenzyme Q10 and zinc are included in the composition according to the invention. These compositions may serve as additives or potentiators, thus increasing the cholesterol lowing effect of phytosterols and/or phytostanols, and/or for teament and prevention of vascular disorders. Preferred polyunsaturated fatty acids are omega-6-fatty acids or omega-3-fatty acids or mixtures thereof, for example eicosapentaenoic acid, docosahexaenoic acid or linoleic acid. As a preferred antioxidant, a tocopherol, for example vitamin E, is used. As a preferred phospholipid, lecithin is used.

[0040] According to an even further preferred embodiment, long chain polyunsaturated fatty acids, phospholipids and a compound selected from the group of folic acid, vitamin B12, vitamin B6, magnesium, zinc are included in composition for use in reduction of blood serum cholesterol levels or prevention of elevated blood serum cholesterol levels.

[0041] The composition according to the invention is preferably administered orally. The composition can for example be added to food or feed products such as beverages or products with a substantial oil content or ingested as nutritional supplement in the form of for example tablet, capsule, microbead, emulsion, powder, granule, suspension, syrup, elixir, chewing gums and the like.

[0042] Preferred daily intake amounts of the components according to the invention greatly depend on the concentration of available and/or active component present in the composition. This is especially applicable for the plant-derived material capable of inhibiting cholesterol biosynthesis and the composition capable of increasing cholesterol metabolism, According to a preferred embodiment, the daily dose of the composition according to the invention includes about 0.01 to 5 gram phytosterol and/or phytostanol or mixtures thereof, more preferably about 0.1 to 1 gram, most preferred about 0.2 to 0.6 gram. The composition capable of inhibiting cholesterol biosynthesis preferably comprises per daily dose about 0.01 to about 30 gram, depending on the type of herbal preparation used. For example, when using crude preparations of *Polygonum multiflorum*, e.g. unprocessed root, the daily intake is preferably between about 0.5 gram and about 15 gram. When processed *Polygonum multiflorum* is used (the process for preparation of processed *Polygonum multiflorum* is well known in the art and reduces LD50 value of *Polygonum multiflorum* compared to crude *Polygonm multiflorum*), the daily intake is preferably between about 0.5 gram and about 30 gram. According to a preferred embodiment of this invention, concentrated

extracts of one or more of the plant sources are used. According to a further preferred embodiment, a concentrated extract of *Polygonumn mutiflorum* is used, corresponding to about 0.5 to out 30 gram crude *Polygonum multiflorum*, preferably about 3-10 gram crude *Polygonum muliflorum*. Thus when using an aqueous extract having an concentration ratio of 16:1 (16 times concentrated), the daily intake is preferably about 0,05 gram to about 2 grams, even more preferably about 0.1 gram to about 0.7 gram of the extract.

[0043] The composition capable of increasing cholesterol metabolism preferably comprises per daily dose about 0.01 to about 30 gram depending on the type of herbal preparation used. For example, when using crude preparations of *Chrysanthemum morifolium*, e.g. unprocessed flower, the daily intake is preferably about 1 gram to about 15 gram. According to a preferred embodiment, a concentrated extract of *Chrysanthemum morifolium* is used corresponding to about 1-15 grain crude *Chrysanthemum morifolium*, preferably about 3-10 gram crude *Chrysanthemum morifolium*. Thus when using an aqueous extract of *Chysanthemum morifolium* having an concentration ratio of about 10:1 (10 times concentrated), the daily -intke is preferably about 0.01 gram to about 3 grams, even more preferably about 0.1 gram to about 0.7 gram of the extract.

EXAMPLE 1

Capsule Comosition I

[0044] A capsule comprising:

[0045] 500 mg phytosterol mixture; including about brapsicasterol (6%), campesterol (30%), stigmasterol (22%), sitosterol (58%).

[0046] 250 mg concentrated Radix Polygoni multiflora water extract with concentration ratio of 16:1 (obtainable form P. L. Thomas & Co,, Inc, having adress Morristown, N.J. 07980)

[0047] 200 mg Flos Chrysanthemi extract (obtainable form MTC Nutricions, Inc, Whitestone, N.Y. 11357)

EXAMPLE 2

Capsule Composition II

[0048] A capsule comprising:

[0049] 500 mg phytosterol mixture; including about brassicasterol (6%), campesterol (30%), stigmasterol (22%), sitosterol (580%).

[0050] 250 mg Radix Polygoni multiflora extract

[0051] 200 mg Flos Chrysanthlemi extact

[0052] 400 mg lecithin

[0053] 60 mg eicosapentacnoic acid

[0054] 60 mg docosahexaenoic acid

EXAMPLE 3

Capsule Composition III

[0055] The capsule described in example 1, further comprising:

[0056] 1000 mg soybean oil

[0057] 150 mg lauric acid and monoolein.

EXAMPLE 4

Capsule Composition TV

[0058] The capsule described in example 2, further comprising:

[0059] 400 IU vitaniin B.

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We claim:

1. A composition comprising;

a. one or more phytosterols and/or phytostanols or a mixture thereof capable of reducing cholesterol absorption in the intestine;

b. a composition capable of inhibiting cholesterol biosynthesis;

c. a composition capable of increasing cholesterol metabolism, wherein at least one of compositions b. and c. is derived from plants.

2. A composition according to claim 1, wherein the at least one of compositions b. and c. is an extract from a plant or plant parts.

3. A composition according to claim 2, wherein compositions b. and c. are e from different plants or parts thereof.

4. A composition according to claim 1, wherein composition b. capable of inhibiting cholesterol biosynthesis comprises one or more HMG-CoA reductase inhibitors and/or squalene synthase inhibitors.

5. A composition according to claim 4, wherein the composition capable of inhibiting cholesterol biosynthesis comprises one or more HMG-CoA reductase inhibitors.

6. A composition according to claim 4, wherein the composition capable of inhibiting cholesterol biosynthesis is derived from a plant or plant part selected from *Alisma orientale*, Typha spp., *Salvia mittiorhiza, Polygonum multiflorum*, Curcuma spp., Ligusticum spp., Polygonatum spp., *Polygonum cuspidatum*; Corydatis spp; *Chrysanthemum morifolium; Arthemisia capillaris; Crataegus pinnatifida, Eleutheroccus senticocus, Astragatus membranaceus* and subspecies and varieties thereof.

7. A composition according to claim 6, wherein the composition capable of inibiting cholesterol biosynthesis is an aqueous extract of *Polygonum multiflorum*.

8. A composition according to claim 1, wherein composition a contains at least 25% by weight of phytosterols and/or phytostmols.

9. A composition according to claim 1, wherein the phytosterol and/or phytostanol or mixture thereof comprises a plant sterol obtained from vegetable oil or wood pulp.

10. A composition according to claim 9, comprising a phytosterol selected from sitosterol, stigmasterol, ergosterol, campesterol, avenasterol, brassicasterol, desmosterol, chalinosterol, poriferasterol, clionasterol sitostanol, stigmastanol and campestanol, and in particular comprises a sitosterol.

11. A composition according to claim 1, wherein composition c. capable of increasing cholesterol metabolism comprises an effective amount of a composition capable of increasing conversion of cholesterol into bile acids and/or inhibiting the esterification of cholesterol.

12. A composition according to claim 11, wherein composition c. comprises one or more cholesterol 7α-hydroxylase activators and/or one or more Acyl-CoA acyl transferase inhibitors.

13. A composition according to claim 12, wherein the composition capable of increasing cholesterol metabolism is derived from a plant or plant part selected from *Polygonum muliflorum, Polygonum cuspidatum*, Curcuma spp., Ligusticum spp., Polygontum spp., Corydalis spp., *Chrysanthemum morifolium, Arthemisia capillaris* and *Acanthopanax senthcosus*.

14. A composition according to claim 13, wherein the composition comprising an effective amount of a composition capable of increasing cholesterol metabolism is an aqueous extract of *Chrysanthemum morifolium*.

15. A composition according to claim 1, further comprising an effective amount of a component for the prevention and/or treatment of vascular disorders.

16. A composition according to claim 15, wherein the component for the prevention and/or treatment of vascular disorders is selected from polyunsaturated fatty adds, antioxidants, phospholipids, folic acid, vitamin B12, vitamin B6, magnesium, coenzyme Q10 and zinc.

17. A composition according to claim 16, wherein the polyunsaturated fatty acids comprise omega-6-fatty acids and/or omega-3-fatty acids.

18. A composition according to claim 16, wherein the phospholipids comprise lecithin.

19. A composition according to claim 16, wherein the antioxidants comprise tocopherols.

20. A composition according to claim 19, wherein the tocopherols comprise vitamin E.

21. A food or beverage product comprising a composition according to claim 1.

22. A nutritional supplement comprising a composition according to claim 1.

23. A tablet, capsule, microbead, emulsion, powder, granule, suspension, syrup, elixir or chewing gum comprising a composition according to claim 1.

24. A method of reducing serum cholesterol levels or preventing elevated blood serum cholesterol levels comprising administering to a person an effective amount of a composition comprising:

a. one or more phytosterols and/or phytostanols or a mixture thereof capable of reducing cholesterol absorption in the intestine,

b. a plantderived composition capable of inhibiting cholesterol biosynthesis; and

c. a plant-derived composition capable of increasing cholesterol metabolism.

* * * * *

US006440399B1

(12) **United States Patent**
Gers-Barlag et al.

(10) **Patent No.: US 6,440,399 B1**
(45) **Date of Patent: *Aug. 27, 2002**

(54) **EMULSIFIER-FREE FINELY DISPERSED SYSTEMS OF THE WATER-IN-OIL TYPE**

(75) Inventors: **Heinrich Gers-Barlag**, Kummerfeld; **Anja Müller**, Rümpel, both of (DE)

(73) Assignee: **Beiersdorf AG**, Hamburg (DE)

(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.

This patent is subject to a terminal disclaimer.

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§ 371 (c)(1),
(2), (4) Date: **Feb. 9, 2000**

(87) PCT Pub. No.: **WO98/42300**

PCT Pub. Date: **Oct. 1, 1998**

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Mar. 25, 1997 (DE) 197 12 483

(51) **Int. Cl.**[7] **A61K 7/42**
(52) **U.S. Cl.** **424/59**; 424/401
(58) **Field of Search** 424/59

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(74) *Attorney, Agent, or Firm*—Norris McLaughlin & Marcus

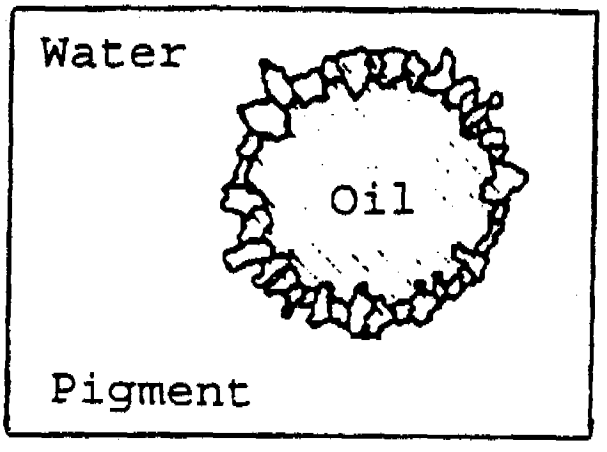
(57) **ABSTRACT**

Emulsifier-free cosmetic or dermatological preparations, which are finely dispersed systems of the oil-in-water type, comprising

1. an oil phase,
2. an aqueous phase and
3. one or more types of micronized, inorganic pigments which
   a) have an average particle size of less than 200 nm, and whose particles
   b) have both hydrophilic and lipophilic properties, i.e. have an amphiphilic character, and thus position themselves at the water/oil interface, and which
   c) are selected from the group consisting of metal oxides, which
   d) are optionally coated on the surface

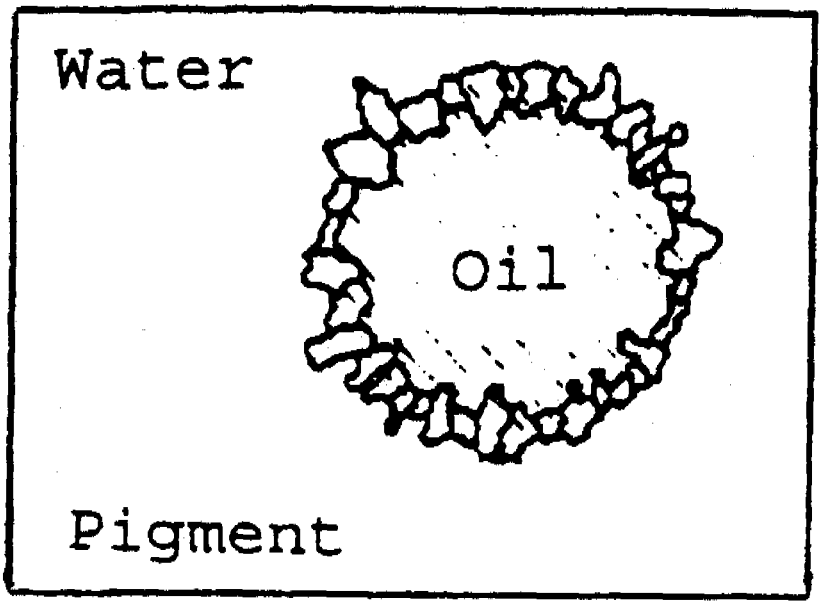
and also optionally comprising further cosmetic or pharmaceutical auxiliaries, additives and/or active ingredients.

10 Claims, 1 Drawing Sheet



O/W Pickering emulsion

Figure 1



O/W Pickering emulsion

EMULSIFIER-FREE FINELY DISPERSED SYSTEMS OF THE WATER-IN-OIL TYPE

This application is a 371 of PCT/EP98/01661, which was filed on Mar 21, 1998.

The present invention relates to emulsifier-free finely dispersed systems of the oil-in-water type, preferably as cosmetic or dermatological preparations.

Emulsions are generally taken to mean hetero-geneous systems which consist of two liquids which are immiscible or have only limited miscibility with one another, which are usually referred to as phases. In an emulsion, one of the two liquids is dispersed in the form of very fine droplets in the other liquid.

If the two liquids are water and oil and if oil droplets are finely dispersed in water, then this is an oil-in-water emulsion (O/W emulsion, e.g. milk). The basic character of a O/W emulsion is defined by the water. In a water-in-oil emulsion (W/O emulsion, e.g. butter), the principle is reversed, the base character here being determined by the oil.

In order to achieve permanent dispersion of one liquid in another, emulsions in the traditional sense require the addition of an interface-active ingredient (emulsifier). Emulsifiers have an amphiphilic molecular structure, consisting of a polar (hydrophilic) and a non-polar (lipophilic) molecular moiety, which are spatially separate from one another. In simple emulsions, finely dispersed droplets of one phase, surrounded by an emulsifier shell, (water droplets in W/O emulsions or lipid vesicles in O/W emulsions) are present in the second phase. Emulsifiers lower the interfacial tension between the phases by positioning themselves at the interface between the two liquids. At the phase boundary, they form oil/water interfacial films, which prevent irreversible coalescence of the droplets. Emulsions are frequently stabilized using emulsifier mixtures.

Traditional emulsifiers can, depending on their hydrophilic molecular moiety, be divided into ionic (anionic, cationic and amphoteric) and nonionic:
the most well known example of an anionic emulsifier is soap, which is usually the term used for the water-soluble sodium salts or potassium salts of saturated or unsaturated higher fatty acids.

Important examples of cationic emulsifiers are quaternary ammonium compounds.

The hydrophilic molecular moiety of nonionic emulsifiers frequently consists of glycerol, polyglycerol, sorbitans, carbohydrates and polyoxyethylene glycols, and, in most cases, is linked to the lipophilic molecular moiety via ester and ether bonds. The lipophilic molecular moiety usually consists of fatty alcohols, fatty acids or isofatty acids. By varying the structure and the size of the polar and nonpolar molecular moiety, the lipophilicity and hydrophilicity of the emulsifiers can be varied within wide limits.

A decisive factor for the stability of an emulsion is the correct choice of emulsifiers. The characteristics of all substances present in the system are to be taken into consideration. In the case of, for example, skin care emulsions, polar oil components and, for example, UV filters lead to instability. As well as the emulsifiers, therefore, other stabilizers are also used which, for example, increase the viscosity of the emulsion and/or act as a protective colloid.

Emulsions are an important type of product in the field of cosmetic and/or dermatological preparations.

Cosmetic preparations are essentially used for skin care. The main aim of skin care in the cosmetics sense is to strengthen or rebuild the skin's natural function as a barrier

against environmental influences (e.g. dirt, chemicals, microorganisms) and against the loss of endogenous substances (e.g. water, natural fats, electrolytes). If this function becomes impaired, increased resorption of toxic or allergenic substances or infection by microorganisms may result, leading to toxic or allergic skin reactions.

Another aim of skin care is to compensate for the loss by the skin of grease and water caused by daily washing. This is particularly important if the natural regeneration ability is inadequate. Furthermore, skin care products should protect against environmental influences, in particular against sun and wind, and delay skin ageing.

Cosmetic preparations are also used as deodorants. Such formulations are used to control body odour which is produced when fresh sweat, which is in itself odourless, is decomposed by microorganisms.

Medicinal topical compositions usually comprise one or more medicaments in an effective concentration. For the sake of simplicity, in order to distinguish clearly between cosmetic and medicinal use and corresponding products, reference is made to the legal provisions in the Federal Republic of Germany (e.g. Cosmetics Regulation, Foods and Drugs Act).

The use of customary emulsifiers in cosmetic or dermatological preparations is in itself acceptable. Nevertheless, emulsifiers, like ultimately any chemical substance, may in certain circumstances cause allergic reactions or reactions based on oversensitivity of the user.

For example, it is known that certain light dermatoses are triggered by certain emulsifiers, but also by a variety of fats and simultaneous exposure to sunlight. Such light dermatoses are also called "Mallorca acne". There has thus been no lack of attempts to reduce the amount of customary emulsifiers to a minimum, in the ideal case even to zero.

A reduction in the required amount of emulsifier can, for example, be achieved by taking advantage of the fact that very finely divided solid particles have an additional stabilizing action. The solid substance accumulates at the oil/water phase boundary in the form of a layer, as a result of which coalescence of the dispersed phases is prevented. It is not the chemical properties of the solid particles which are of fundamental importance here, but the surface properties.

Around 1910, Pickering prepared paraffin/water emulsions which were stabilized merely by the addition of various solids, such as basic copper sulphate, basic iron sulphate or other metal sulphates. This type of emulsion is thus also referred to as a Pickering emulsion. For this type of emulsion, Pickering postulated the following conditions:

(1) The solid particles are only suitable for stabilization if they are significantly smaller than the droplets of the inner phase and do not have a tendency to form agglomerates.

(2) An important property of an emulsion-stabilizing solid is also its wettability. I.e. in order to stabilize an O/W emulsion, the solid has, for example, to be more readily wettable by water than by oil.

The original forms of Pickering emulsions initially surfaced, as it were, as undesired secondary effects in a variety of industrial processes, such as, for example, in secondary oil recovery, the extraction of bitumen from tar sand and other separation processes involving two immiscible liquids and fine, dispersed solid particles. These are generally W/O emulsions which are stabilized by mineral solids. Accordingly, investigation of corresponding systems, such as, for example, the oil/water/soot or oil/water/slate dust systems was initially the focus of research activity.

Basic experiments have shown that one characteristic of a Pickering emulsion is that the solid particles are arranged

at the interface between the two liquid phases where they form, as it were, a mechanical barrier against the mixing of the liquid droplets.

It is a relatively new technical development to use Pickering emulsions as a base for cosmetic or dermatological preparations.

One way of achieving solids stabilization in a cosmetic or dermatological preparation is, according to May-Alert (*Pharmazie in unserer Zeit* [*Pharmacy in our time*], Vol. 15, 1986, No. 1, 1–7) for example, to use emulsifier mixtures which contain both anionic and cationic surfactants. Since mixing anionic and cationic surfactants produces precipitates of insoluble, electro-neutral compounds, deliberate precipitation of these neutral surfactants in the oil/water interface makes it possible to achieve additional solids stabilization in the sense of a Pickering emulsion.

EP-A-0 686 391 describes water-in-oil emulsions which are free from surface-active ingredients and are stabilized only by solids. Stabilization is achieved here using spherical polyalkylsilsesquioxane particles which have a diameter of from 100 nm up to 20 μm. According to the above, these emulsions can be referred to as Pickering emulsions.

In addition to the described Pickering emulsions, the prior art describes further emulsifier-free, finely dispersed cosmetic or dermatological preparations which are generally referred to as hydrodispersions. Hydrodispersions are dispersions of a liquid, semi-solid or solid internal (discontinuous) lipid phase in an outer aqueous (continuous) phase. Hydrodispersions, like other emulsions, are metastable systems and therefore have a tendency to convert into a state of two mutually coherent discrete phases.

In the case of hydrodispersions of a liquid lipid phase in an outer aqueous phase, stability can be ensured, for example, by constructing, in the aqueous phase, a gel structure in which the lipid droplets are stably suspended. DE-A 44 25 268 describes stable finely dispersed, emulsifier-free cosmetic or dermatological preparations of the oil-in-water type, which, in addition to one oil phase and one water phase, comprise one or more thickeners from the group consisting of acrylic polymers, polysaccharides and alkyl ethers thereof, where these thickeners must not cause any lowering of the interfacial tension.

The object of the present invention was to extend the prior art to include cosmetic or dermatological preparations of the oil-in-water type, in which it is not necessary to use any emulsifiers of a conventional type.

Surprisingly, this object is achieved by emulsifier-free cosmetic or dermatological preparations which are finely dispersed systems of the oil-in-water type, comprising

1. an oil phase,
2. an aqueous phase and
3. one or more types of micronized, inorganic pigments which
   a) have an average particle size of less than 200 nm, and whose particles
   b) have both hydrophilic and lipophilic properties, i.e. have an amphiphilic character, and thus position themselves at the water/oil interface, and which
   c) are selected from the group consisting of metal oxides, which
   d) are optionally coated on the surface and also

optionally comprising further cosmetic or pharmaceutical auxiliaries, additives and/or active ingredients.

The amphiphilic character of the inorganic pigments according to the invention is evident, for example, from the fact that the latter are dispersible both in water and in oil.

German laid-open specification 43 03 983 discloses cosmetic or dermatological light protection formulations which are based on hydrodispersions and comprise inorganic micropigments as UV filter substances, the formulations consisting of an inner lipid phase and an outer aqueous phase and being essentially free from emulsifiers. However, the inorganic micropigments are incorporated into the lipid phase of the hydrodispersion and act as UV absorbers or UV reflectors. This prior art document was therefore unable to indicate the route to the present invention.

The preparations according to the invention are mixtures of oils or oil-soluble substances and water or water-soluble components, which are stabilized by adding micronized solids particles and which do not contain an emulsifier in the traditional sense. One way of explaining the stability of these preparations is that the pigment particles—as shown diagrammatically in FIG. 1—attach themselves to the droplets of the disperse phase and form, as it were, a mechanical barrier, which prevents coalescence of the droplets.

The preparations according to the invention are extremely satisfactory preparations in every respect, whose aqueous/fatty phase ratio can be varied within extraordinarily wide limits and, in addition, have the advantage over the prior art that large amounts of oils can be stably incorporated in water.

The fatty phase content of the formulations according to the invention is preferably chosen from the range of from 0.5 to 75% by weight, based on the total weight of the formulations.

It is advantageous to choose the average particle diameter of the pigments used to be between 1 nm and 200 nm, particularly advantageously between 5 nm and 100 nm.

It is essentially insignificant for the present invention in which of the potentially naturally occurring modifications the metal oxides are present.

It is advantageous for the purposes of the present invention to stabilize Pickering emulsions using untreated, virtually pure pigment particles, in particular those which can also be used as dye in the food industry and/or as absorber of UV radiation in sunscreens. Examples of advantageous pigments are titanium dioxide pigments and/or zinc oxide pigments, which are available under the trade names KRONOS® 1171 (TiO_2) from Kronos Titan, as well as zinc oxide neutral from Haarmann & Reimer and NanoX (ZnO) from Harcros Chemical Group.

For the purposes of the present invention, Pickering emulsions are advantageously stabilized by inorganic pigments which have been surface-treated (coated) to repel water, it being the intention that the amphiphilic character is simultaneously formed or retained. This surface-treatment may involve providing the pigments with a thin hydrophobic layer by processes known per se.

One such process, which is described below using titanium dioxide as an example, consists in, for example, producing the hydrophobic surface layer according to the following reaction

$$n\mathrm{TiO_2}+m(\mathrm{RO})_3\mathrm{Si}\text{—}R' \rightarrow n\mathrm{TiO_2}\ (\mathrm{surf.})$$

n and m are arbitrary stoichiometric parameters, and R and R' are the desired organic radicals. Particularly advantageous pigments are TiO_2 pigments, for example those coated with aluminium stearate and available under the trade name MT 100 T from TAYCA.

Another advantageous coating of the inorganic pigments consists of dimethylpolysiloxane (also: dimethicone), a mixture of completely methylated, linear siloxane polymers which have been terminally blocked with trimethylsiloxy units. Zinc oxide pigments which have been coated in this way are particularly advantageous for the purposes of the present invention.

It is also advantageous to coat the inorganic pigments with a mixture of dimethylpolysiloxane, in particular dimethylpolysiloxane having an average chain length of from 200 to 350 dimethylsiloxane units, and silica gel which is also referred to as simethicone. It is particularly advantageous for the inorganic pigments to be additionally coated with aluminium hydroxide or aluminium oxide hydrate (also: alumina, CAS No.: 1333-84-2). Titanium dioxides which have been coated with simethicone and alumina are particularly advantageous, in which case the coating can also comprise water. One example thereof is the titanium dioxide obtainable under the trade name Eusolex T2000 from Merck.

For the purposes of the present invention, Pickering emulsions are also particularly advantageously stabilized by metal oxide particles coated with aluminium hydroxide and/or silicon dioxide. Advantageous examples are titanium dioxide particles which are available under the name EUSOLEX® TA from Merck.

In all of the above cases it is advantageous to choose the concentration of the pigments to be greater than 0.1% by weight, particularly advantageously between 0.1% and 30% by weight, based on the total weight of the preparations.

The Pickering emulsions according to the invention can be used as bases for cosmetic or dermatological formulations. These can have the customary composition and be used, for example, for the treatment and care of the skin, as lip care product, as deodorant and as make-up or make-up remover product in decorative cosmetics or as light protection preparation. For use, the cosmetic and dermatological preparations according to the invention are applied to the skin in sufficient amount in the manner customary for cosmetics.

Accordingly, for the purposes of the present invention, cosmetic or topical dermatological compositions may, depending on their structure, be used, for example, as skin-protection cream, cleansing milk, sunscreen lotion, nutrient cream, day or night cream, etc. Where appropriate, it is possible and advantageous to use the compositions according to the invention as bases for pharmaceutical formulations.

The cosmetic and dermatological preparations according to the invention may comprise cosmetic auxiliaries, as customarily used in such preparations, e.g. preservatives, bactericides, perfumes, antifoams, dyes, pigments which have a colouring effect, thickeners, plasticizers, moisturizing and/or moisture-retaining substances, fats, oils, waxes or other customary constituents of a cosmetic or dermatological formulation, such as alcohols, polyols, polymers, foam stabilizers, electrolytes, organic solvents or silicone derivatives.

Pickering emulsions according to the invention may advantageously also comprise thickeners to improve the tactile properties of the emulsion and/or to establish a suitable viscosity. Examples of advantageous thickeners are starch derivatives, cellulose derivatives, carbopols, xanthan gum and phyllosilicates. The use of hydroxyethylcellulose, which is available, for example, under the trade name NATROSOL PLUS 330 CS from Aqualon, is particularly advantageous.

In particular, the Pickering emulsions according to the invention may also comprise antioxidants. According to the invention, favourable antioxidants which can be used are any antioxidants suitable or conventional for cosmetic and/or dermatological applications.

The antioxidants are advantageously selected from the group consisting of amino acids (e.g. glycine, histidine, tyrosine, tryptophan) and their derivatives, imidazoles, (e.g. urocanic acid) and their derivatives, peptides, such as D,L-carnosine, D-carnosine, L-carnosine and their derivatives (e.g. anserine), carotenoids, carotenes (e.g. α-carotene, β-carotene, lycopene) and their derivatives, chlorogenic acid and its derivatives, lipoic acid and its derivatives (e.g. dihydrolipoic acid), aurothioglucose, propylthiouracil and other thiols (e.g. thioredoxin, glutathione, cysteine, cystine, cystamine and their glycosyl, N-acetyl, methyl, ethyl, propyl, amyl, butyl and lauryl, palmitoyl, oleyl, γ-linoleyl, cholesteryl and glyceryl esters) and their salts, dilauryl thiodipropionate, distearyl thiodipropionate, thiodipropionic acid and its derivatives (esters, ethers, peptides, lipids, nucleotides, nucleosides and salts) and sulphoximine compounds (e.g. buthionine sulphoximines, homocysteine sulphoximine, buthionine sulphones, penta-, hexa-, heptathionine sulphoximines) in very low tolerated doses (e.g. pmol to μmol/kg), and also (metal) chelating agents (e.g. α-hydroxyfatty acids, palmitic acid, phytic acid, lactoferrin), α-hydroxy acids (e.g. citric acid, lactic acid, malic acid), humic acid, bile acid, bile extracts, bilirubin, biliverdin, EDTA, EGTA and their derivatives, unsaturated fatty acids and their derivatives (e.g. γ-linolenic acid, linoleic acid, oleic acid), folic acid and its derivatives, ubiquinone and ubiquinol and their derivatives, vitamin C and derivatives (e.g. ascorbyl palmitate, Mg ascorbyl phosphate, ascorbyl acetate), tocopherols and derivatives (e.g. vitamin E acetate), vitamin A and derivatives (vitamin A palmitate) and coniferyl benzoate of benzoin, rutinic acid and its derivatives, α-glycosylrutin, ferulic acid, furfurylideneglucitol, carnosine, butylated hydroxytoluene, butylated hydroxyanisole, nordihydroguaiac acid, nordihydroguaiaretic acid, trihydroxybutyrophenone, uric acid and its derivatives, mannose and its derivatives, zinc and its derivatives (e.g. ZnO, $ZnSO_4$), selenium and its derivatives (e.g. selenomethionine), stilbenes and their derivatives (e.g. stilbene oxide, trans-stilbene oxide), and the derivatives (salts, esters, ethers, sugars, nucleotides, nucleosides, peptides and lipids) of said active ingredients which are suitable according to the invention.

The amount of the abovementioned antioxidants (one or more compounds) in the preparations according to the invention is preferably from 0.001 to 30% by weight, particularly preferably from 0.05 to 20% by weight, in particular 1–10% by weight, based on the total weight of the preparation.

If vitamin E and/or its derivatives are used as the antioxidant or antioxidants, their respective concentrations are advantageously chosen from the range of 0.001–10% by weight, based on the total weight of the formulation.

If vitamin A or vitamin A derivatives or carotenes or their derivatives are used as the antioxidant or antioxidants, their respective concentrations are advantageously chosen from the range of 0.001–10% by weight, based on the total weight of the formulation.

Cosmetic and dermatological preparations which are in the form of a sunscreen are also favourable. These preferably comprise at least one UV-A filter substance and/or at least one UV-B filter substance and/or at least one further inorganic pigment selected from the group consisting of the oxides of iron, zirconium, silicon, manganese, aluminium, cerium and mixtures thereof and also modifications in which the oxides are the active agents.

For the purposes of the present invention, it is, however, also advantageous to provide such cosmetic and dermatological preparations whose main purpose is not protection against sunlight, but which nevertheless comprise sub-

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Señor
SUPERINTENDENTE DE INDUSTRIA Y COMERCIO
DIVISION DE NUEVAS CREACIONES
E. S. D.

Re: P1.-**UNILEVER N.V.-** Solicitud de patente de Invención en Fase Nacional PCT para **"EMULSION AGUA EN ACEITE QUE COMPRENDE ESTEROLESTERES"-** Clase **A23L 1/30.-** Expediente No. **05-040.025.-**

1. Me refiero a mi memorial de 10 de Enero de 2006.

2. Por medio del presente atentamente ruego a usted, se sirva pronunciarse en relación con la solicitud arriba nombrada, ya que desde el **31 de Agosto de 2005**, esto hace ya casi dos **(2) años**, que fue publicado el extracto de la presente solicitud en la Gaceta de la Propiedad Industrial No. 555 y el examen de patentabilidad correspondiente fue solicitado en su debido momento mediante memorial de 10 de Enero de 2006, sin que haya sido adelantado ningún otro trámite.

3. Cabe anotar que esta demora en el trámite acarrea grave perjuicio para mi representado.

Señor Superintendente,

ALICIA LLOREDA RICAURTE
T.P. 53.215

NRB/fegv

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DIVISION DE NUEVAS CREACIONES

RADICACIÓN EXPEDIENTE No 05-40025

EL EXTRACTO DE LA PRESENTE SOLICITUD DE **PATENTE DE INVENCION**

FUE PUBLICADO EN LA GACETA DE PROPIEDAD INDUSTRIAL No **555** DE

FECHA **31** DE **AGOSTO** DEL **2005**, EL TERMINO HABIL SEÑALADO POR LA

LEY EXPIRA EL **28** DE **NOVIEMBRE** DEL **2005**

NOTA: Dentro del plazo de los seis (6) meses siguientes a partir de la fecha de publicación en la gaceta de Propiedad Industrial, deberá solicitar y cancelar el examen de patentabilidad so pena de que la solicitud caiga en abandono, de acuerdo con lo establecido en el Artículo 44 de la Decisión 486/2000.

SE PRESENTARON OPOSICIONES POR PARTE DE TERCEROS.

SI _ ___ NO__ _ **X** _ ___

US 20020068095A1

(19) **United States**

(12) **Patent Application Publication** (10) **Pub. No.: US 2002/0068095 A1**

Qi et al. (43) **Pub. Date: Jun. 6, 2002**

(54) **CHOLESTEROL LOWERING SUPPLEMENT**

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(57) **ABSTRACT**

The invention provides a composition and a method for lowering blood serum cholesterol levels or for preventing elevated blood serum cholesterol levels, as well as suitable composition comprising (a) one or more phytosterols and/or phytostanols or a mixture thereof capable of reducing cholesterol absorption in the intestine, (b) a composition capable of inhibiting cholesterol biosynthesis, and (c) a composition capable of increasing cholesterol metabolism, wherein at least one of compositions b. and c. is preferably derived from plants.

CHOLESTEROL LOWERING SUPPLEMENT

BACKGROUND OF THE INVENTION

[0001] Cardiovascular diseases (CVD) are the major cause of death and disability in the United States and other industrialized countries despite recent declines in CVD mortality rates, They account for more deaths annually than any other disease, including all forms of cancer combined[i]. In the USA more than 1 million heart attacks occur each year and more than half a million people still die as a result. This enormous toll has focused attention on the possible prevention of CVD by various means, especially through lowering of plasma cholesterol levels. It is well established now that elevated total cholesterol, and in particular low-density lipoprotein (LDL) cholesterol, in plasma plays an important role in the development of atherosclerosis[ii]. Clinical trials have demonstrated clearly that decreasing cholesterol concentrations in plasma can contribute to primary and secondary prevention of coronary events and mortality.[iii] Some studies have estimated a 2% reduction in risk of a coronary artery event by a 1% reduction of total serum cholesterol.[iv]

[0002] Serum cholesterol levels can for example be lowered by a daily intake of some components similar to cholesterol. The components similar to cholesterol reduce the absorption of cholesterol from the intestines into the bloodstream.

[0003] U.S. Pat. No. 5,958,913 discloses a substance comprising a sawed sterol fatty acid ester capable of lowering LDL cholesterol levels in serum and which is fat soluble. The substance can be taken orally as a food additive, food substitute or supplement A daily consumption of saturated sterol fatty acid ester in an mount between about 0.2 and about 20 g/day has been shown to reduce the absorption of endogenic cholesterol.

[0004] Alternatively, compositions that inhibit the cholesterol biosynthesis, for example by inhibiting enzyme 3-hydroxy-3-methylglutaryl coenzyme A reductase (HMG-CoA reductase), an enzyme involved in the cholesterol biosynthesis, can lower blood serum cholesterol by slowing down the production of cholesterol. It is believed that inhibition of HIMG-CoA reductase results in a reduction in hepatic cholesterol synthesis and intracellular cholesterol stores, a compensatory increase in low-density lipoprotein (LDL) receptors, and a subsequent enhanced removal of LDL-cholesterol from plasma. Potent inhibitors of HMG-CoA reductase include for example the compounds referred to as statins, which family comprises for example lovastatin, pravastatin and fluvastatin.

[0005] Several studies suggested a HMG-CoA reductase iniibiting effect of plant extracts. Wang et al.[v] demonstrated HMG-CoA reductase inhibition by several aqueous plant extracts in isolated rat hepatic niicrosomal preparations. In vivo studies on rats demonstrated the inhibitory effect of traditional Chinese herbs on the cholesterol biosynthesis[vi].

[0006] An enzyme involved in the cholesterol metabolism (conversion of cholesterol into other components) is cholesterol 7α-hydroxylase. Hepatic cholesterol 7α-hydroxylase catalyses the conversion of cholesterol into 7α cholesterol, which is believed to be the rate limiting step in conversion of cholesterol into bile acids. It has been suggested that the increase of cholesterol 7α-hydroxylase activity results in the decrease of blood serum cholesterol and thus is an important pathway of elimination of cholesterol from the body. Methods for treatment of blood serum cholesterol related disorders by inhibition of cholesterol 7α hydroxylase are known in the art.

[0007] WO 91/15213 discloses a method for treatment of cholesterol gallstones employing side-chain hydroxylated cholesterol derivative. In particular the method for treatment of cholesterol gallstones involves ale administration of 25- or 26-hydroxycholesterol, which enhance the activity of cholesterol 7α-hydroxylase, thereby inhibiting for example cholesterol precipitation. Additionally, Wang et al.[vi] showed that several herbal preparations are capable of increasing cholesterol 7α hydroxylase activity.

[0008] According to Raicht et al.[vii], feeding cholesterol to rats increased cholesterol absorption from 1.2 to 70 mg/day and inhibited its synthesis in the liver and enhanced conversion of cholesterol to bile acids from 13.7 to 27.3 mg/day. Furthermore, when given cholesterol to the rats, HMG-CoA reductase activity was inhibited 80%. With beta-sitosterol, cholesterol absorption was inhibited but cholesterol synthesis was increased from 20.0 to 28.8 mg/day.

[0009] The majority of cholesterol lowering compositions currently known in the art include ingredients which either lower cholesterol absorption within the intestines or inhibit cholesterol biosynthesis, e.g., by inhibition of HMG-CoA reductase. As Raicht et al.[vii] demonstrated, the inhibition of cholesterol absorption in the intestine (using β-sitosterol) lowers cholesterol absorption, however, the inhibition of cholesterol absorption in the intestines is followed by an increase in HMG-CoA reductase activity. Increase of the HMG-CoA reductase activity is likely to increase cholesterol biosynthesis and thereby reduce the net effect of cholesterol absorption inhibitors. It is therefore desirable to decrease serum cholesterol levels using combination compositions, which reduce cholesterol absorption within the intestine and additionally inhibit cholesterol biosynthesis, e.g. by inhibiting HMG-CoA reductase activity,

[0010] Methods of reducing plasma cholesterol levels comprising administering a combination of an effective amount of cholesterol biosynthesis inhibitor and an effective amount of cholesterol absorption inhibitor are disclosed in U.S. Pat. No. 5,661,145. The administered combination includes a beta-lactam cholesterol absorption inhibitor and a HMG-CoA reductase inhibitor, which can for example be a statin, for example lovastatin or pravastatin. Other pharmaceutical combination compositions including certain cholesterol absorption inhibitors and cholesterol synthesis inhibitors useful for the treatment of hypercholesterolemia and atherosclerosis are described in U.S. Pat. No. 5,807,834.

[0011] WO 98/01759 describes a method of determining in animal the ratio of serum campesterol to the level of β-sitosterol comprising several steps. Additionally, a combination composition for enhancing in an animal the inhibitory effect of phytostrols on cholesterol enterocyte absorption, which comprises one or more phytosterols which inhibit predominantly one or both of cholesterol and beta sitosterol and one or more compounds which limit cholesterol synthesis, e.g. compounds selected form HMG CoA reductase inhibitors, for example lovostatin, is described. Further described is the main disadvantage of the above composition i.e. the use of statins, and the critical side effects related with the use of statins.

[0012] WO 00/15201 discloses a composition for preventing and treating CVD containing phytosterols or phytostanols as agents inhibiting cholesterol absorption and tocotrienols as agents suppressing cholesterol biosynthesis.

[0013] WO 00/38725 provides combinations of cardiovascular therapeutic compounds for the prophylaxis or treatment of cardiovascular disease including hypercliolesterolemia and atherosclerosis. Combinations disclosed include an ileal bile acid transport inhibitor combined with a cholesteryl ester transport protein inhibitor, a fibric acid derivative, a nicotinic acid derivative, a microsomal triglyceride transfer protein inhibitor, a cholesterol absorption antagonist, or others. Further combinations include a CETP inhibitor with a fibric acid derivative, a nicotinic acid derivative, a bile acid sequestrant, a microsomal triglyceride transfer protein inhibitor, a cholesterol absorption antagonist, or others.

[0014] U.S. Pat. No. 5,958,417 describes a herbal combination comprising Crataegus, Ho Shou Wu, Cassia Seed, Chrysanthemum, Lotus Leaf, Alisma, Hu-Zhang, and Rhubarb wherein the herbs are present in specific weight percentages. However, the herbal combination lacks a potent cholesterol absorption-inhibiting component, such as an effective amount of phytosterol and/or phytostanol.

[0015] Notwithstanding these disclosures, there remains a need in the art for compositions for use in reduction of blood serum cholesterol levels or prevention of elevated blood serum cholesterol levels. Combination compositions including cholesterol absorption inhibitors and cholesterol synthesis inhibitors useful for reduction of blood serum cholesterol levels known in the art are mostly chemically manufactured compositions and the known compositions are therefore undesirable for many people, not natural and costly.

[0016] Additionally, the combination compositions known in the art cannot be used frequently for a longer period since negative side effects will occur. Recent studies have indicated that drugs like statins, often used as HMG-CoA reductase inhibitors in combination compositions, and fibrates can be carcinogenic or cause other undesirable side effects. Newman et al[viii] reported that all members of the classes stains and fibrates cause cancer in rodents. Furthermore, two hyperlipidemic patients treated with simvastatin, a potent inhibitor of HMG-CoA reductase, experienced cheilitis after beginning treatment The rash resolved after discontinuation of medication and subsequent treatment with topical moisturizers and topical corticosteroids (Mebregan et al.[ix]). Khosla et al[x] alerts clinicians to the possible adverse effect of simvastati s and other statins by reporting a case of a 79-year-old man who had onset of fatigue, myalgia, and pleuritic chest pain 3 months after initiation of therapy with simvastatin. Lovastatin was reported to cause liver failure (Tolman[xi]).

[0017] Furthermore, combination compositions known in the art to date only comprise effective amounts of at most two of the blood serum cholesterol reducing activities, selected from reduction of cholesterol absorption in the intestine, inhibition cholesterol of biosynthesis and increase of cholesterol metabolism.

SUMMARY OF THE INVENTION

[0018] The invention disclosed here takes away the above problems and provides combination compositions for use in reduction of blood serum cholesterol levels or prevention of elevated blood serum cholesterol levels comprising one or more phytosterols and/or phytostanols or mixtures thereof capable of reducing cholesterol absorption in the intestine, an effective amount of a plant derived composition capable of Inhibiting cholesterol biosynthesis and an effective amount of a plant derived composition capable of increasing cholesterol metabolism.

[0019] The combination composition disclosed here fulfills the need for cholesterol-reducing combinations having plant-derived active components. The composition according to the invention can therefore be administered for a longer period, thus making it suitable for use in compositions for reduction of blood serum cholesterol levels or prevention of elevated blood serum cholesterol levels. The invention provides a balanced composition for use in reducing blood serum cholesterol levels or preventing elevated blood cholesterol levels. These combination compositions avoid the potential side effects or compensator effects associated with the administration of relatively high levels of components solely directed at reducing cholesterol absorption in the intestine or at inhibiting cholesterol synthesis or at increasing cholesterol metabolism or at only two of those three mechanisms.

[0020] The present invention provides a composition for use in reduction of blood serum cholesterol levels or prevention of elevated blood serum cholesterol levels comprising:

[0021] a. one or more phytosterols and/or phytostanols or mixtures thereof capable of reducing cholesterol absorption in the intestine

[0022] b. an effective mount of a composition capable of inhibiting cholesterol biosynthesis

[0023] c. an effective amount of a composition capable of increasing cholesterol metabolism.

[0024] Advantageously, at least one of compositions b. and c. is derived from plants, i.e. obtained by extraction of plants, Preferably, both composition b. and composition c. are derived from plants, most preferably from different plants or different combinations of plants.

[0025] A further object of the present invention is to provide a method of reducing serum cholesterol levels or preventing elevated blood serum cholesterol levels comprising, administrating to a person a composition comprising one or more phytosterols and/or phytostanols or mixtures thereof capable of reducing cholesterol absorption in the intestine, an effective amount of a plant derived composition capable of inhibiting cholesterol biosynthesis and an effective amount of a plant derived composition capable of increasing cholesterol metabolism.

DESCRIPTION OF THE INVENTION

[0026] The term clolesterol biosynthesis is well known to those skilled in tie art and generally refers to the biochemical pathways of cholesterol synthesis within the animal (e.g. human) body. The term cholesterol metabolism is also well known to those skilled in the art and generally refers to the biochemical pathways involved in the removal of cholesterol from he body.

[0027] The phytosterol and/or phytostanol or mixtures thereof capable of reducing cholesterol absorption in the intestine can be any composition of phytosterol and/or phytostanol or mixtures thereof known in the art and having a cholesterol absorption reducing effect, Phytosterols are steroids derived from plants, yeasts or fungi, which have a hydroxyl group at C-3 and no other functional groups and differ from animal sterols, in particular cholesterol, in that the side chain at position 17 contains a double bond and/or an additional methyl, ethyl or ethylidene group, in particular at position 24. The term phytosterol and/or phytostanol according to the invention, comprises all such analogues, which may further have a double bond at the 5-position in the cyclic unit as in most natural phytosterols, or one or more double bonds at other positions (e.g. 6, 7, 8(9), 8(14), 14, 5/7, or no double bonds in the cyclic unit as in the stanols, or even additionl methyl groups as e.g. in α_1-sitosterol; the term includes natural phytosterols and derivatives thereof.

[0028] According to a preferred embodiment the phytosterol and/or phytostnols or us thereof are obtained from vegetable oil or wood pulp. More in particular, α-, β-, γ-sitostwol, stigmasterol, ergosterol, campesterol, avenasterol, brassicasterol, desmosterol, chalinosterol, poriferasterol, clionasterol, sitostanol, stigmastanol, campestol or a mixture of one or more of the above phytosterols or phytostanols is used. According to an even more preferred embodiment, sitosterol or mixtures including a sitosterol are used, The concentration of phytosterols andor phytostanols in composition a. is at least 10%, preferably at least 25%, more preferably at least 50%, most preferably at least 80% by dry weight of composition a.

[0029] The plant derived composition capable of inhibiting cholesterol biosynthesis according to the invention preferably comprises a composition capable of inhibiting the enzyme 3-hydroxy-3-methylglutaryl coenzyme A reductase (HMG-CoA reduase inhibitor) and/or inhibiting squalene synthase (squalene synthase inhibitor), HMG-CoA reductase inhibitors can decrease the activity of HMG-CoA reductase, thus inhibiting the conversion of HMG-CoA to mevalonate. The HMG-CoA reductase inhibitors can act on the HMG-CoA reductase directly or indirectly by decreasing the activity of one or more enzymes (e.g. HMG-CoA reductase phosphatse) or cofactors involved in the activation of HMG-CoA reductase or increasing the activity of one or more enzymes (e.g. HMG-CoA reductase kinase) or cofactors involved in the down regulation of HMG-CoA reductase or by decreasing the of HMG-CoA redactase gene transcription or of HMG-CoA reductase RNA translation.

[0030] Squalene synthase inhibitors can decrease the activity of squalene synthase, thus inhibiting the conversion of farnesyl pyrophosphate into squalene. Squalene synthase inhibitors can act on the squalene synthase directly, or indirectly by decreasing the activity of one or more enzymes or cofactors involved in the activation of squalene synthase; or increasing the activity of one or more enzymes or cofactors involved in the down regulation of squalene synthase; or decreasing the squalene synthase gene transcription or squalene synthase RNA translation. According to a preferred embodiment the composition capable of inhibiting cholesterol biosynthesis comprises one or more HMG-CoA reductase inhibitors.

[0031] The composition capable of inhibiting cholesterol biosynthesis is preferably obtained from whole plants or from one or more parts thereof, for example stems, stalks, roots, shoots, rhizomes, tubers, fruits, foliage, kernels, husks, hulls or mixtures thereof, Preferably, the composition is an extract from whole plants or plat parts. Such extracts can be obtained by harvesting the plants, optionally comminuting the plants and/or separating certain parts of the plants, drying, extracting the plats or plant parts using liquid extraction, and optionally concentrating the extract. Drying of the plants is usually necessary to avoid degradation of labile components or microbial contamination upon storage, transport or processing, and results in lowering the water content from e.g. 50-90% to e.g. less than 25%., preferably less than 20%, most preferably between 5 and 15%. Drying is performed under mild conditions i.e. at temperatures between 0 and 80° C., in particular between 10 and 60° C., or by freeze-drying. Before or after drying, the plants or plant parts may be reduced in particle size to coarse fragments or even to fine powder by processes such as grinding, flaking or mincing. Grinding using a hammer mill or equivalent machine is preferred. Extraction according to the invention refers to separating the desired plant material by physical or chemical means, preferably with the aid of a solvent. Suitable solvents include water, water-alcohol mixtures, alcohols, ethers, hydrocarbons or other organic solvents or mixtures thereof Water and water-based solvent mixtures are preferred. Extraction can be performed by maceration, i.e. soaking for a time between e.g. one minute and several hours, optionally using agitation, followed by filtration. For larger scale operations, counter-current extraction can be used. The resulting solutions can be concentrated to liquid or solid extracts using e.g. tin layer evaporators, freeze-drying or spray-drying techniques. Spray-drying resulting in concentrated to dry powders is preferred. Suitable plant extracts containing inhibitors of cholesterol biosynthesis are commercially available.

[0032] Preferred sources for the composition capable of hinibitig cholesterol biosynthesis include *Alisma orientale* (pharmaceutical name Rhizoma alismatis); Typha spp., for example *Typha angustifolia* or *Typha orientalis* (pharmaceutical name Pollen Typhea); *Salvia miltiorhiza* (pharmaceutical name Radix salviae mniltiorrhizae); *Polygonum mulliflorum* (pharmaceutical name Radix Polygoni multiflora); Curcuma spp., for example *C. kwangsiensis, C. longa, C. phaecaulis, C. wenyuin* or *C. aromatica*, (pharmaceutical name Radix curcmae or Rhizoma curcumae); Ligusticum spp., for example *L. wallichii*, (pharmaceutical name Rhizoma Ligustici); Polygonatum spp., for example *P. kingianum, P. sibiricum* or *P. cyrtonema* (pharmaceutical name Rhizoma polygonati); *Polygonum cuspidatum* (pharmaceutical name Rhizoma polygoni cuspidati); Corydalis spp, (pharmaceutical name Rhizoma Corydalis); *Chrysanthemum morifolium* (pharmaceutical name Flos Chrysathemi); *Arthemisia capillaris* (pharmaceutical name Herba Arimisiae capillaris); *Crataegus pinnatifida* or its variations or subspecies pharmaceutical name Fructus Crataegi pinnatifidae); *Eleutheroccus senticocus* (pharmaceutical name Radix eleutherococci senticosi); *Astragalus membranaceus* (pharmaceutical name Radix Astragali). According to a particularly preferred embodiment *Polygonum multiflorum* is used as a source for tile composition capable of inhibiting cholesterol biosynthesis, more preferably at aqueous extract of *Polygonum multiflorum*.

[0033] Preferably, the composition capable of increasing cholesterol metabolism increases the conversion of choles-

terol into bile acids and/or inhibits the esterification of cholesterol. According to an even more preferred embodiment, the composition capable of increasing cholesterol metabolism enhances the activity of cholesterol 7α-hydroxylase (cholesterol-7α hydroxylase activator) and/or inhibits the activity of Acyl-CoA acyl transferase (Acyl-CoA acyl transferase inhibitor).

[0034] A cholesterol 7α-hydroxylase activator can enhance the activity of cholesterol 7α-hydroxylase, thus enhance the conversion of cholesterol into 7α-cholesterol. Cholesterol 7α-hydroxylase activators can act on the cholesterol 7α-hydroxylase directly or indirectly by increasing the activity of enzymes and cofactors involved in the activation of cholesterol 7α-hydroxylase or decrease the activity of enzymes or cofactors involved in the down-regulation of cholesterol 7α-hydroxylase (e.g. by effecting enzymes involved in the phosphorylation and dephosphorylation of cholesterol 7α-hydroxylase) or increasing the cholesterol 7α-hydroxylase gene transcription or cholesterol 7α hydroxylase RNA translation.

[0035] Acyl-CoA acyl transferase inhibitors can inhibit the conversion of cholesterol into cholesteryl oleate. Acyl-CoA acyl transferase inhibitors can act on tile Acyl-CoA acyl transferase directly, or indirectly by decreasing the activity of one or more enzymes or cofictors involved in the activation of Acyl-CoA acyl transferase or increasing the activity of one or more enzymes or cofactors involved in the down regulation of Acyl-CoA acyl transferase or decreasing the Acyl-CoA acyl transferase gene transcription or Acyl-CoA acyl tslerase RNA translation. According to a preferred embodiment, the composition capable of increasing cholesterol metabolism comprises one or more cholesterol 7a-hydroxylase activators, which act systemically.

[0036] The composition capable of enhancing cholesterol metabolism is preferably obtained from whole plants or from one or more parts thereof, for example stems, stalks, roots, shoots, rhizomes, tubers, fruits, foliage, kernels, husks, hulls or mixtures thereof. The whole plants or plant parts providing enhancers of cholesterol metabolism may be subjected to extraction as described above for plants providing inhibitors of cholesterol biosynthesis, Suitable extracts containing the plant-derived metabolic enhancers are commercially available.

[0037] Preferred sources for obtaining the compositions capable of increasing cholesterol metabolism include *Polygonum multiflorum* (pharmaceutical name Radix Polygoni multiflora); Curcuma spp., for example *C. kwangsiensis, C. longa, C. phaecaulis, C. wenyuin* or *C. aromatica*, pharmaceutical name Radix curcumae or Rhizoma curcumae); Ligusticum spp., for example *L. wallichii*, (pharmaceutical name Rhizoma Ligustici); Polygonatum spp., for example *P. kingianum, P. sibiricum* or *P. cyrtonema* (pharmaceutical name Rhizoma polygonati); *Polygonum cuspidatum* (pharmaceutical name Rhizoma polygoni cuspidati); Corydalis spp. (pharmaceutical name Rhizoma Corydalis); *Chrysanthemum morifolium* (pharmaceutical name Flos Chrysanthemi); *Arthemisia capillaris* (pharmaceutical name Herba Artimisiae capillaris); *Acanthopanax senticosus* (pharmaceutical name Radix Astragali). According to a particularly preferred embodiment *Chrysanthemum morfolium* is used as a source for the composition capable of increasing cholesterol metabolism, more preferably an aqueous extract *Chrysanthemum morifolium.*

[0038] The dry weight ratio between composition a. and the combination of compositions b. and c. is preferably between 0:1 and 1:10, more preferably between 4:1 and 1:4. The dry weight ratio between compositions b. and c, is preferably between 10:1 and 1:10, more preferably between 3:1 and 1:3.

[0039] Elevated serum cholesterol levels are often closely related to a reduced vascular health. It is therefore advantageously to include in the composition for use in reduction of blood serum cholesterol levels or prevention of elevated blood serum cholesterol levels, an effective amount of a composition for the prevention and/or treatment of vascular disorders. Preferably one or more compounds selected from the group of polyunsaturated fatty acids, antioxidants, phospholipids, folic acid, vitamin B12, vitamin B6, magnesium, coenzyme Q10 and zinc are included in the composition according to the invention. These compositions may serve as additives or potentiators, thus increasing the cholesterol lowing effect of phytosterols and/or phytostanols, and/or for teament and prevention of vascular disorders. Preferred polyunsaturated fatty acids are omega-6-fatty acids or omega-3-fatty acids or mixtures thereof, for example eicosapentaenoic acid, docosahexaenoic acid or linoleic acid. As a preferred antioxidant, a tocopherol, for example vitamin E, is used. As a preferred phospholipid, lecithin is used.

[0040] According to an even further preferred embodiment, long chain polyunsaturated fatty acids, phospholipids and a compound selected from the group of folic acid, vitamin B12, vitamin B6, magnesium, zinc are included in composition for use in reduction of blood serum cholesterol levels or prevention of elevated blood serum cholesterol levels.

[0041] The composition according to the invention is preferably administered orally. The composition can for example be added to food or feed products such as beverages or products with a substantial oil content or ingested as nutritional supplement in the form of for example tablet, capsule, microbead, emulsion, powder, granule, suspension, syrup, elixir, chewing gums and the like.

[0042] Preferred daily intake amounts of the components according to the invention greatly depend on the concentration of available and/or active component present in the composition. This is especially applicable for the plant-derived material capable of inhibiting cholesterol biosynthesis and the composition capable of increasing cholesterol metabolism, According to a preferred embodiment, the daily dose of the composition according to the invention includes about 0.01 to 5 gram phytosterol and/or phytostanol or mixtures thereof, more preferably about 0.1 to 1 gram, most preferred about 0.2 to 0.6 gram. The composition capable of inhibiting cholesterol biosynthesis preferably comprises per daily dose about 0.01 to about 30 gram, depending on the type of herbal preparation used. For example, when using crude preparations of *Polygonum multiflorum*, e.g. unprocessed root, the daily intake is preferably between about 0.5 gram and about 15 gram. When processed *Polygonum multiflorum* is used (the process for preparation of processed *Polygonum multiflorum* is well known in the art and reduces LD50 value of *Polygonum multiflorum* compared to crude *Polygonm multiflorum*), the daily intake is preferably between about 0.5 gram and about 30 gram. According to a preferred embodiment of this invention, concentrated

extracts of one or more of the plant sources are used. According to a further preferred embodiment, a concentrated extract of *Polygonumn mutiflorum* is used, corresponding to about 0.5 to out 30 gram crude *Polygonum multiflorum*, preferably about 3-10 gram crude *Polygonum muliflorum*. Thus when using an aqueous extract having an concentration ratio of 16:1 (16 times concentrated), the daily intake is preferably about 0,05 gram to about 2 grams, even more preferably about 0.1 gram to about 0.7 gram of the extract.

[0043] The composition capable of increasing cholesterol metabolism preferably comprises per daily dose about 0.01 to about 30 gram depending on the type of herbal preparation used. For example, when using crude preparations of *Chrysanthemum morifolium*, e.g. unprocessed flower, the daily intake is preferably about 1 gram to about 15 gram. According to a preferred embodiment, a concentrated extract of *Chrysanthemum morifolium* is used corresponding to about 1-15 grain crude *Chrysanthemum morifolium*, preferably about 3-10 gram crude *Chrysanthemum morifolium*. Thus when using an aqueous extract of *Chysanthemum morifolium* having an concentration ratio of about 10:1 (10 times concentrated), the daily -intke is preferably about 0.01 gram to about 3 grams, even more preferably about 0.1 gram to about 0.7 gram of the extract.

EXAMPLE 1

Capsule Comosition I

[0044] A capsule comprising:

[0045] 500 mg phytosterol mixture; including about brapsicasterol (6%), campesterol (30%), stigmasterol (22%), sitosterol (58%).

[0046] 250 mg concentrated Radix Polygoni multiflora water extract with concentration ratio of 16:1 (obtainable form P. L. Thomas & Co,, Inc, having adress Morristown, N.J. 07980)

[0047] 200 mg Flos Chrysanthemi extract (obtainable form MTC Nutricions, Inc, Whitestone, N.Y. 11357)

EXAMPLE 2

Capsule Composition II

[0048] A capsule comprising:

[0049] 500 mg phytosterol mixture; including about brassicasterol (6%), campesterol (30%), stigmasterol (22%), sitosterol (580%).

[0050] 250 mg Radix Polygoni multiflora extract

[0051] 200 mg Flos Chrysanthlemi extact

[0052] 400 mg lecithin

[0053] 60 mg eicosapentaenoic acid

[0054] 60 mg docosahexaenoic acid

EXAMPLE 3

Capsule Composition III

[0055] The capsule described in example 1, further comprising:

[0056] 1000 mg soybean oil

[0057] 150 mg lauric acid and monoolein.

EXAMPLE 4

Capsule Composition TV

[0058] The capsule described in example 2, further comprising:

[0059] 400 IU vitaniin B.

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[0061] [ii] Cholesterol Adult Treatment Panel: Report of the National Cholesterol Education Program Expert Panel on Detection, Evaluation and Treatment of High Cholesterol in Adults, Arch. Intern. Med., 1988, 148, 36-69.

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[0070] [xi] Tolman K. G., Defining patient risks from expanded preventive therapies. Am, J. Cardiol, 2000, 85(12A): 15E-9E.

We claim:

1. A composition comprising;

a. one or more phytosterols and/or phytostanols or a mixture thereof capable of reducing cholesterol absorption in the intestine;

b. a composition capable of inhibiting clholesterol biosynthesis;

c. a composition capable of increasing cholesterol metabolism, wherein at least one of compositions b. and c. is derived from plants.

2. A composition according to claim 1, wherein the at least one of compositions b. and c. is an extract from a plant or plant parts.

3. A composition according to claim 2, wherein compositions b. and c. are e from different plants or parts thereof.

4. A composition according to claim 1, wherein composition b. capable of inhibiting cholesterol biosynthesis comprises one or more HMG-CoA reductase inhibitors and/or squalene synthase inhibitors.

5. A composition according to claim 4, wherein the composition capable of inhibiting cholesterol biosynthesis comprises one or more HMG-CoA reductase inhibitors.

6. A composition according to claim 4, wherein the composition capable of inhibiting cholesterol biosynthesis is derived from a plant or plant part selected from *Alisma orientale*, Typha spp., *Salvia mittiorhiza, Polygonum multiflorum*, Curcuma spp., Ligusticum spp., Polygonatum spp., *Polygonum cuspidatum*; Corydatis spp; *Chrysanthemum morifolium; Arthemisia capillaris; Crataegus pinnatifida, Eleutheroccus senticocus, Astragatus membranaceus* and subspecies and varieties thereof.

7. A composition according to claim 6, wherein the composition capable of inibiting cholesterol biosynthesis is an aqueous extract of *Polygonum multiflorum*.

8. A composition according to claim 1, wherein composition a contains at least 25% by weight of phytosterols and/or phytostmols.

9. A composition according to claim 1, wherein the phytosterol and/or phytostanol or mixture thereof comprises a plant sterol obtained from vegetable oil or wood pulp.

10. A composition according to claim 9, comprising a phytosterol selected from sitosterol, stigmasterol, ergosterol, campesterol, avenasterol, brassicasterol, desmosterol, chalinosterol, poriferasterol, clionasterol sitostanol, stigmastanol and campestanol, and in particular comprises a sitosterol.

11. A composition according to claim 1, wherein composition c. capable of increasing cholesterol metabolism comprises an effective amount of a composition capable of increasing conversion of cholesterol into bile acids and/or inhibiting the esterification of cholesterol.

12. A composition according to claim 11, wherein composition c. comprises one or more cholesterol 7α-hydroxylase activators and/or one or more Acyl-CoA acyl transferase inhibitors.

13. A composition according to claim 12, wherein the composition capable of increasing cholesterol metabolism is derived from a plant or plant part selected from *Polygonum muliflorum, Polygonum cuspidatum*, Curcuma spp., Ligusticum spp., Polygontum spp., Corydalis spp., *Chrysanthemum morifolium, Arthemisia capillaris* and *Acanthopanax senthcosus*.

14. A composition according to claim 13, wherein the composition comprising an effective amount of a composition capable of increasing cholesterol metabolism is an aqueous extract of *Chrysanthemum morifolium*.

15. A composition according to claim 1, further comprising an effective amount of a component for the prevention and/or treatment of vascular disorders.

16. A composition according to claim 15, wherein the component for the prevention and/or treatment of vascular disorders is selected from polyunsaturated fatty adds, antioxidants, phospholipids, folic acid, vitamin B12, vitamin B6, magnesium, coenzyme Q10 and zinc.

17. A composition according to claim 16, wherein the polyunsaturated fatty acids comprise omega-6-fatty acids and/or omega-3-fatty acids.

18. A composition according to claim 16, wherein the phospholipids comprise lecithin.

19. A composition according to claim 16, wherein the antioxidants comprise tocopherols.

20. A composition according to claim 19, wherein the tocopherols comprise vitamin E.

21. A food or beverage product comprising a composition according to claim 1.

22. A nutritional supplement comprising a composition according to claim 1.

23. A tablet, capsule, microbead, emulsion, powder, granule, suspension, syrup, elixir or chewing gum comprising a composition according to claim 1.

24. A method of reducing serum cholesterol levels or preventing elevated blood serum cholesterol levels comprising administering to a person an effective amount of a composition comprising:

a. one or more phytosterols and/or phytostanols or a mixture thereof capable of reducing cholesterol absorption in the intestine,

b. a plantderived composition capable of inhibiting cholesterol biosynthesis; and

c. a plant-derived composition capable of increasing cholesterol metabolism.

* * * * *

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Gers-Barlag et al.

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(45) **Date of Patent: *Aug. 27, 2002**

(54) **EMULSIFIER-FREE FINELY DISPERSED SYSTEMS OF THE WATER-IN-OIL TYPE**

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(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.

This patent is subject to a terminal disclaimer.

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(58) **Field of Search** 424/59

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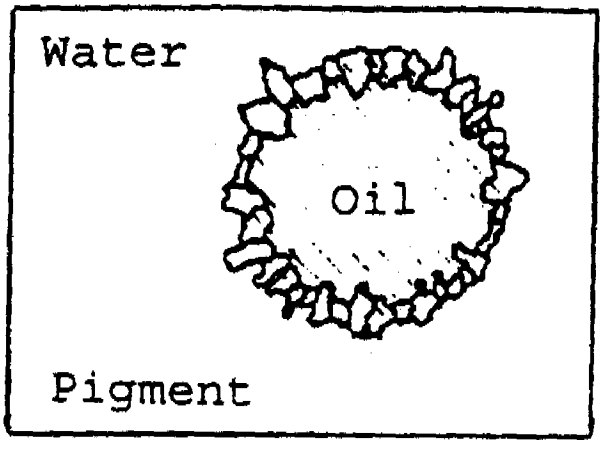
(57) **ABSTRACT**

Emulsifier-free cosmetic or dermatological preparations, which are finely dispersed systems of the oil-in-water type, comprising

1. an oil phase,
2. an aqueous phase and
3. one or more types of micronized, inorganic pigments which
   a) have an average particle size of less than 200 nm, and whose particles
   b) have both hydrophilic and lipophilic properties, i.e. have an amphiphilic character, and thus position themselves at the water/oil interface, and which
   c) are selected from the group consisting of metal oxides, which
   d) are optionally coated on the surface

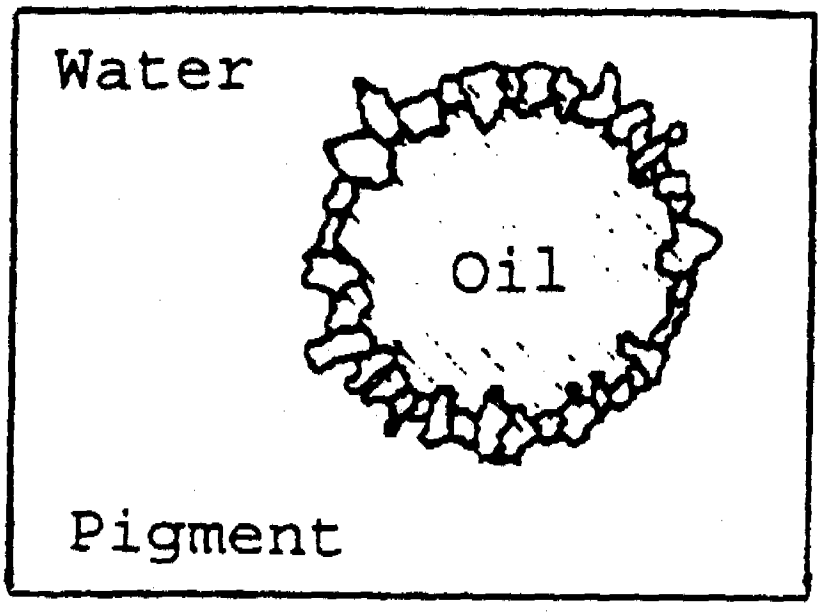
and also optionally comprising further cosmetic or pharmaceutical auxiliaries, additives and/or active ingredients.

10 Claims, 1 Drawing Sheet



O/W Pickering emulsion

Figure 1



O/W Pickering emulsion

EMULSIFIER-FREE FINELY DISPERSED SYSTEMS OF THE WATER-IN-OIL TYPE

This application is a 371 of PCT/EP98/01661, which was filed on Mar 21, 1998.

The present invention relates to emulsifier-free finely dispersed systems of the oil-in-water type, preferably as cosmetic or dermatological preparations.

Emulsions are generally taken to mean hetero-geneous systems which consist of two liquids which are immiscible or have only limited miscibility with one another, which are usually referred to as phases. In an emulsion, one of the two liquids is dispersed in the form of very fine droplets in the other liquid.

If the two liquids are water and oil and if oil droplets are finely dispersed in water, then this is an oil-in-water emulsion (O/W emulsion, e.g. milk). The basic character of a O/W emulsion is defined by the water. In a water-in-oil emulsion (W/O emulsion, e.g. butter), the principle is reversed, the base character here being determined by the oil.

In order to achieve permanent dispersion of one liquid in another, emulsions in the traditional sense require the addition of an interface-active ingredient (emulsifier). Emulsifiers have an amphiphilic molecular structure, consisting of a polar (hydrophilic) and a non-polar (lipophilic) molecular moiety, which are spatially separate from one another. In simple emulsions, finely dispersed droplets of one phase, surrounded by an emulsifier shell, (water droplets in W/O emulsions or lipid vesicles in O/W emulsions) are present in the second phase. Emulsifiers lower the interfacial tension between the phases by positioning themselves at the interface between the two liquids. At the phase boundary, they form oil/water interfacial films, which prevent irreversible coalescence of the droplets. Emulsions are frequently stabilized using emulsifier mixtures.

Traditional emulsifiers can, depending on their hydrophilic molecular moiety, be divided into ionic (anionic, cationic and amphoteric) and nonionic:
the most well known example of an anionic emulsifier is soap, which is usually the term used for the water-soluble sodium salts or potassium salts of saturated or unsaturated higher fatty acids.

Important examples of cationic emulsifiers are quaternary ammonium compounds.

The hydrophilic molecular moiety of nonionic emulsifiers frequently consists of glycerol, polyglycerol, sorbitans, carbohydrates and polyoxyethylene glycols, and, in most cases, is linked to the lipophilic molecular moiety via ester and ether bonds. The lipophilic molecular moiety usually consists of fatty alcohols, fatty acids or isofatty acids. By varying the structure and the size of the polar and nonpolar molecular moiety, the lipophilicity and hydrophilicity of the emulsifiers can be varied within wide limits.

A decisive factor for the stability of an emulsion is the correct choice of emulsifiers. The characteristics of all substances present in the system are to be taken into consideration. In the case of, for example, skin care emulsions, polar oil components and, for example, UV filters lead to instability. As well as the emulsifiers, therefore, other stabilizers are also used which, for example, increase the viscosity of the emulsion and/or act as a protective colloid.

Emulsions are an important type of product in the field of cosmetic and/or dermatological preparations.

Cosmetic preparations are essentially used for skin care. The main aim of skin care in the cosmetics sense is to strengthen or rebuild the skin's natural function as a barrier

against environmental influences (e.g. dirt, chemicals, microorganisms) and against the loss of endogenous substances (e.g. water, natural fats, electrolytes). If this function becomes impaired, increased resorption of toxic or allergenic substances or infection by microorganisms may result, leading to toxic or allergic skin reactions.

Another aim of skin care is to compensate for the loss by the skin of grease and water caused by daily washing. This is particularly important if the natural regeneration ability is inadequate. Furthermore, skin care products should protect against environmental influences, in particular against sun and wind, and delay skin ageing.

Cosmetic preparations are also used as deodorants. Such formulations are used to control body odour which is produced when fresh sweat, which is in itself odourless, is decomposed by microorganisms.

Medicinal topical compositions usually comprise one or more medicaments in an effective concentration. For the sake of simplicity, in order to distinguish clearly between cosmetic and medicinal use and corresponding products, reference is made to the legal provisions in the Federal Republic of Germany (e.g. Cosmetics Regulation, Foods and Drugs Act).

The use of customary emulsifiers in cosmetic or dermatological preparations is in itself acceptable. Nevertheless, emulsifiers, like ultimately any chemical substance, may in certain circumstances cause allergic reactions or reactions based on oversensitivity of the user.

For example, it is known that certain light dermatoses are triggered by certain emulsifiers, but also by a variety of fats and simultaneous exposure to sunlight. Such light dermatoses are also called "Mallorca acne". There has thus been no lack of attempts to reduce the amount of customary emulsifiers to a minimum, in the ideal case even to zero.

A reduction in the required amount of emulsifier can, for example, be achieved by taking advantage of the fact that very finely divided solid particles have an additional stabilizing action. The solid substance accumulates at the oil/water phase boundary in the form of a layer, as a result of which coalescence of the dispersed phases is prevented. It is not the chemical properties of the solid particles which are of fundamental importance here, but the surface properties.

Around 1910, Pickering prepared paraffin/water emulsions which were stabilized merely by the addition of various solids, such as basic copper sulphate, basic iron sulphate or other metal sulphates. This type of emulsion is thus also referred to as a Pickering emulsion. For this type of emulsion, Pickering postulated the following conditions:

(1) The solid particles are only suitable for stabilization if they are significantly smaller than the droplets of the inner phase and do not have a tendency to form agglomerates.

(2) An important property of an emulsion-stabilizing solid is also its wettability. I.e. in order to stabilize an O/W emulsion, the solid has, for example, to be more readily wettable by water than by oil.

The original forms of Pickering emulsions initially surfaced, as it were, as undesired secondary effects in a variety of industrial processes, such as, for example, in secondary oil recovery, the extraction of bitumen from tar sand and other separation processes involving two immiscible liquids and fine, dispersed solid particles. These are generally W/O emulsions which are stabilized by mineral solids. Accordingly, investigation of corresponding systems, such as, for example, the oil/water/soot or oil/water/slate dust systems was initially the focus of research activity.

Basic experiments have shown that one characteristic of a Pickering emulsion is that the solid particles are arranged

at the interface between the two liquid phases where they form, as it were, a mechanical barrier against the mixing of the liquid droplets.

It is a relatively new technical development to use Pickering emulsions as a base for cosmetic or dermatological preparations.

One way of achieving solids stabilization in a cosmetic or dermatological preparation is, according to May-Alert (*Pharmazie in unserer Zeit* [*Pharmacy in our time*], Vol. 15, 1986, No. 1, 1–7) for example, to use emulsifier mixtures which contain both anionic and cationic surfactants. Since mixing anionic and cationic surfactants produces precipitates of insoluble, electro-neutral compounds, deliberate precipitation of these neutral surfactants in the oil/water interface makes it possible to achieve additional solids stabilization in the sense of a Pickering emulsion.

EP-A-0 686 391 describes water-in-oil emulsions which are free from surface-active ingredients and are stabilized only by solids. Stabilization is achieved here using spherical polyalkylsilsesquioxane particles which have a diameter of from 100 nm up to 20 μm. According to the above, these emulsions can be referred to as Pickering emulsions.

In addition to the described Pickering emulsions, the prior art describes further emulsifier-free, finely dispersed cosmetic or dermatological preparations which are generally referred to as hydrodispersions. Hydrodispersions are dispersions of a liquid, semi-solid or solid internal (discontinuous) lipid phase in an outer aqueous (continuous) phase. Hydrodispersions, like other emulsions, are metastable systems and therefore have a tendency to convert into a state of two mutually coherent discrete phases.

In the case of hydrodispersions of a liquid lipid phase in an outer aqueous phase, stability can be ensured, for example, by constructing, in the aqueous phase, a gel structure in which the lipid droplets are stably suspended. DE-A 44 25 268 describes stable finely dispersed, emulsifier-free cosmetic or dermatological preparations of the oil-in-water type, which, in addition to one oil phase and one water phase, comprise one or more thickeners from the group consisting of acrylic polymers, polysaccharides and alkyl ethers thereof, where these thickeners must not cause any lowering of the interfacial tension.

The object of the present invention was to extend the prior art to include cosmetic or dermatological preparations of the oil-in-water type, in which it is not necessary to use any emulsifiers of a conventional type.

Surprisingly, this object is achieved by emulsifier-free cosmetic or dermatological preparations which are finely dispersed systems of the oil-in-water type, comprising

1. an oil phase,
2. an aqueous phase and
3. one or more types of micronized, inorganic pigments which
   a) have an average particle size of less than 200 nm, and whose particles
   b) have both hydrophilic and lipophilic properties, i.e. have an amphiphilic character, and thus position themselves at the water/oil interface, and which
   c) are selected from the group consisting of metal oxides, which
   d) are optionally coated on the surface and also

optionally comprising further cosmetic or pharmaceutical auxiliaries, additives and/or active ingredients.

The amphiphilic character of the inorganic pigments according to the invention is evident, for example, from the fact that the latter are dispersible both in water and in oil.

German laid-open specification 43 03 983 discloses cosmetic or dermatological light protection formulations which are based on hydrodispersions and comprise inorganic micropigments as UV filter substances, the formulations consisting of an inner lipid phase and an outer aqueous phase and being essentially free from emulsifiers. However, the inorganic micropigments are incorporated into the lipid phase of the hydrodispersion and act as UV absorbers or UV reflectors. This prior art document was therefore unable to indicate the route to the present invention.

The preparations according to the invention are mixtures of oils or oil-soluble substances and water or water-soluble components, which are stabilized by adding micronized solids particles and which do not contain an emulsifier in the traditional sense. One way of explaining the stability of these preparations is that the pigment particles—as shown diagrammatically in FIG. 1—attach themselves to the droplets of the disperse phase and form, as it were, a mechanical barrier, which prevents coalescence of the droplets.

The preparations according to the invention are extremely satisfactory preparations in every respect, whose aqueous/fatty phase ratio can be varied within extraordinarily wide limits and, in addition, have the advantage over the prior art that large amounts of oils can be stably incorporated in water.

The fatty phase content of the formulations according to the invention is preferably chosen from the range of from 0.5 to 75% by weight, based on the total weight of the formulations.

It is advantageous to choose the average particle diameter of the pigments used to be between 1 nm and 200 nm, particularly advantageously between 5 nm and 100 nm.

It is essentially insignificant for the present invention in which of the potentially naturally occurring modifications the metal oxides are present.

It is advantageous for the purposes of the present invention to stabilize Pickering emulsions using untreated, virtually pure pigment particles, in particular those which can also be used as dye in the food industry and/or as absorber of UV radiation in sunscreens. Examples of advantageous pigments are titanium dioxide pigments and/or zinc oxide pigments, which are available under the trade names KRONOS® 1171 (TiO_2) from Kronos Titan, as well as zinc oxide neutral from Haarmann & Reimer and NanoX (ZnO) from Harcros Chemical Group.

For the purposes of the present invention, Pickering emulsions are advantageously stabilized by inorganic pigments which have been surface-treated (coated) to repel water, it being the intention that the amphiphilic character is simultaneously formed or retained. This surface-treatment may involve providing the pigments with a thin hydrophobic layer by processes known per se.

One such process, which is described below using titanium dioxide as an example, consists in, for example, producing the hydrophobic surface layer according to the following reaction

$$n TiO_2 + m(RO)_3Si—R' \rightarrow n TiO_2 \text{ (surf.)}$$

n and m are arbitrary stoichiometric parameters, and R and R' are the desired organic radicals. Particularly advantageous pigments are TiO_2 pigments, for example those coated with aluminium stearate and available under the trade name MT 100 T from TAYCA.

Another advantageous coating of the inorganic pigments consists of dimethylpolysiloxane (also: dimethicone), a mixture of completely methylated, linear siloxane polymers which have been terminally blocked with trimethylsiloxy units. Zinc oxide pigments which have been coated in this way are particularly advantageous for the purposes of the present invention.

It is also advantageous to coat the inorganic pigments with a mixture of dimethylpolysiloxane, in particular dimethylpolysiloxane having an average chain length of from 200 to 350 dimethylsiloxane units, and silica gel which is also referred to as simethicone. It is particularly advantageous for the inorganic pigments to be additionally coated with aluminium hydroxide or aluminium oxide hydrate (also: alumina, CAS No.: 1333-84-2). Titanium dioxides which have been coated with simethicone and alumina are particularly advantageous, in which case the coating can also comprise water. One example thereof is the titanium dioxide obtainable under the trade name Eusolex T2000 from Merck.

For the purposes of the present invention, Pickering emulsions are also particularly advantageously stabilized by metal oxide particles coated with aluminium hydroxide and/or silicon dioxide. Advantageous examples are titanium dioxide particles which are available under the name EUSOLEX® TA from Merck.

In all of the above cases it is advantageous to choose the concentration of the pigments to be greater than 0.1% by weight, particularly advantageously between 0.1% and 30% by weight, based on the total weight of the preparations.

The Pickering emulsions according to the invention can be used as bases for cosmetic or dermatological formulations. These can have the customary composition and be used, for example, for the treatment and care of the skin, as lip care product, as deodorant and as make-up or make-up remover product in decorative cosmetics or as light protection preparation. For use, the cosmetic and dermatological preparations according to the invention are applied to the skin in sufficient amount in the manner customary for cosmetics.

Accordingly, for the purposes of the present invention, cosmetic or topical dermatological compositions may, depending on their structure, be used, for example, as skin-protection cream, cleansing milk, sunscreen lotion, nutrient cream, day or night cream, etc. Where appropriate, it is possible and advantageous to use the compositions according to the invention as bases for pharmaceutical formulations.

The cosmetic and dermatological preparations according to the invention may comprise cosmetic auxiliaries, as customarily used in such preparations, e.g. preservatives, bactericides, perfumes, antifoams, dyes, pigments which have a colouring effect, thickeners, plasticizers, moisturizing and/or moisture-retaining substances, fats, oils, waxes or other customary constituents of a cosmetic or dermatological formulation, such as alcohols, polyols, polymers, foam stabilizers, electrolytes, organic solvents or silicone derivatives.

Pickering emulsions according to the invention may advantageously also comprise thickeners to improve the tactile properties of the emulsion and/or to establish a suitable viscosity. Examples of advantageous thickeners are starch derivatives, cellulose derivatives, carbopols, xanthan gum and phyllosilicates. The use of hydroxyethylcellulose, which is available, for example, under the trade name NATROSOL PLUS 330 CS from Aqualon, is particularly advantageous.

In particular, the Pickering emulsions according to the invention may also comprise antioxidants. According to the invention, favourable antioxidants which can be used are any antioxidants suitable or conventional for cosmetic and/or dermatological applications.

The antioxidants are advantageously selected from the group consisting of amino acids (e.g. glycine, histidine, tyrosine, tryptophan) and their derivatives, imidazoles, (e.g. urocanic acid) and their derivatives, peptides, such as D,L-carnosine, D-carnosine, L-carnosine and their derivatives (e.g. anserine), carotenoids, carotenes (e.g. α-carotene, β-carotene, lycopene) and their derivatives, chlorogenic acid and its derivatives, lipoic acid and its derivatives (e.g. dihydrolipoic acid), aurothioglucose, propylthiouracil and other thiols (e.g. thioredoxin, glutathione, cysteine, cystine, cystamine and their glycosyl, N-acetyl, methyl, ethyl, propyl, amyl, butyl and lauryl, palmitoyl, oleyl, γ-linoleyl, cholesteryl and glyceryl esters) and their salts, dilauryl thiodipropionate, distearyl thiodipropionate, thiodipropionic acid and its derivatives (esters, ethers, peptides, lipids, nucleotides, nucleosides and salts) and sulphoximine compounds (e.g. buthionine sulphoximines, homocysteine sulphoximine, buthionine sulphones, penta-, hexa-, heptathionine sulphoximines) in very low tolerated doses (e.g. pmol to μmol/kg), and also (metal) chelating agents (e.g. α-hydroxyfatty acids, palmitic acid, phytic acid, lactoferrin), α-hydroxy acids (e.g. citric acid, lactic acid, malic acid), humic acid, bile acid, bile extracts, bilirubin, biliverdin, EDTA, EGTA and their derivatives, unsaturated fatty acids and their derivatives (e.g. γ-linolenic acid, linoleic acid, oleic acid), folic acid and its derivatives, ubiquinone and ubiquinol and their derivatives, vitamin C and derivatives (e.g. ascorbyl palmitate, Mg ascorbyl phosphate, ascorbyl acetate), tocopherols and derivatives (e.g. vitamin E acetate), vitamin A and derivatives (vitamin A palmitate) and coniferyl benzoate of benzoin, rutinic acid and its derivatives, α-glycosylrutin, ferulic acid, furfurylideneglucitol, carnosine, butylated hydroxytoluene, butylated hydroxyanisole, nordihydroguaiac acid, nordihydroguaiaretic acid, trihydroxybutyrophenone, uric acid and its derivatives, mannose and its derivatives, zinc and its derivatives (e.g. ZnO, $ZnSO_4$), selenium and its derivatives (e.g. selenomethionine), stilbenes and their derivatives (e.g. stilbene oxide, trans-stilbene oxide), and the derivatives (salts, esters, ethers, sugars, nucleotides, nucleosides, peptides and lipids) of said active ingredients which are suitable according to the invention.

The amount of the abovementioned antioxidants (one or more compounds) in the preparations according to the invention is preferably from 0.001 to 30% by weight, particularly preferably from 0.05 to 20% by weight, in particular 1–10% by weight, based on the total weight of the preparation.

If vitamin E and/or its derivatives are used as the antioxidant or antioxidants, their respective concentrations are advantageously chosen from the range of 0.001–10% by weight, based on the total weight of the formulation.

If vitamin A or vitamin A derivatives or carotenes or their derivatives are used as the antioxidant or antioxidants, their respective concentrations are advantageously chosen from the range of 0.001–10% by weight, based on the total weight of the formulation.

Cosmetic and dermatological preparations which are in the form of a sunscreen are also favourable. These preferably comprise at least one UV-A filter substance and/or at least one UV-B filter substance and/or at least one further inorganic pigment selected from the group consisting of the oxides of iron, zirconium, silicon, manganese, aluminium, cerium and mixtures thereof and also modifications in which the oxides are the active agents.

For the purposes of the present invention, it is, however, also advantageous to provide such cosmetic and dermatological preparations whose main purpose is not protection against sunlight, but which nevertheless comprise sub-

stances which protect against UV. For example, UV-A and UV-B filter substances are commonly incorporated into day cream.

The preparations according to the invention can advantageously comprise further substances which absorb UV radiation in the UV-B range, the total amount of filter substances being, for example, from 0.1% by weight to 30% by weight, preferably from 0.5 to 10% by weight, in particular from 1 to 6% by weight, based on the total weight of the preparations, in order to provide cosmetic preparations which protect the hair and/or the skin from the whole region of ultraviolet radiation.

If the emulsions according to the invention contain UV-B filter substances, the latter may be oil-soluble or water-soluble. Examples of oil-soluble UV-B filters which are advantageous according to the invention are:

- 3-benzylidenecamphor derivatives, preferably 3-(4-methylbenzylidene)camphor, 3-benzylidene-camphor;
- 4-aminobenzoic acid derivatives, preferably 2-ethylhexyl 4-(dimethylamino)benzoate, amyl 4-(dimethylamino) benzoate;
- Esters of cinnamic acid, preferably 2-ethylhexyl 4-methoxycinnamate, isopentyl 4-methoxycinnamate;
- Esters of salicylic acid, preferably 2-ethylhexyl salicylate, 4-isopropylbenzyl salicylate, homomenthyl salicylate;
- Derivatives of benzophenone, preferably 2-hydroxy-4-methoxybenzophenone, 2-hydroxy-4-methoxy-4'-methylbenzophenone, 2,2'-dihydroxy-4-methoxy-benzophenone;
- Esters of benzalmalonic acid, preferably di (2-ethylhexyl) 4-methoxybenzalmalonate, 2,4,6-tri-anilino(p-carbo-2'ethyl-1'-hexyloxy)-1,3,5-triazine.
- Examples of advantageous water-soluble UV-B filters are:
- Salts of 2-phenylbenzimidazole-5-sulphonic acid, such as its sodium, potassium or its triethanolammonium salt, and also the sulphonic acid itself;
- Sulphonic acid derivatives of benzophenones, preferably 2-hydroxy-4-methoxybenzophenone-sulphonic acid and its salts;
- Sulphonic acid derivatives of 3-benzylidenecamphor, such as e.g. 4-(2-oxo-3-bornylidenemethyl)benzene-sulphonic acid, 2-methyl-5-(2-oxo-3-bornylidene-methyl)sulphonic acid and their salts.

The list of said UV-B filters, which may be used in the Pickering emulsions according to the invention, is of course not intended to be limiting.

It can also be advantageous to use, in the Pickering emulsions according to the invention, UV-A filters which have hitherto been customarily present in cosmetic preparations. These substances are preferably derivatives of dibenzoylmethane, in particular 1-(4'-tert-butylphenyl)-3-(4'-methoxyphenyl)propane-1,3-dione and 1-phenyl-3-(4'-isopropylphenyl)propane-1,3-dione. Preparations which contain the UV-A filters are also provided by the invention. The amounts which may be used are as for the UW-B combination.

Preparations according to the invention can also be advantageously used as bases for cosmetic deodorants and antiperspirants, so that a particular embodiment of the present invention relates to Pickering emulsions as bases for cosmetic deodorants.

Cosmetic deodorants are used to control body odour which arises when fresh sweat, which is in itself odourless, is decomposed by microorganisms. Customary cosmetic deodorants are based on various modes of action.

In antiperspirants, astringents, mainly aluminium salts, such as aluminium hydroxychloride (aluchlorhydrate), reduce sweat production.

The use of antimicrobial substances in cosmetic deodorants can reduce the bacterial flora of the skin. In an ideal situation, only the microorganisms which cause the odour should be effectively reduced. The flow of sweat itself is not influenced as a result, and in ideal circumstances, only microbial decomposition of sweat is stopped temporarily.

The combination of astringents and antimicrobial substances in one and the same composition is also common. Antimicrobial substances are electrolytes and strong Lewis acids, and the incorporation of relatively large amounts of electrolytes and/or Lewis acids into cosmetic and/or dermatological preparations is generally not without problems. Surprisingly, the Pickering emulsions according to the invention are stable even when relatively high concentrations of such active ingredients are used.

O/W Pickering emulsions according to the invention are obtainable by firstly dispersing the pigments in the aqueous phase and then combining the aqueous phase with the fatty phase. Dispersing the pigments firstly in the fatty phase usually gives W/O Pickering emulsions.

The invention thus also provides a process for the preparation of the Pickering emulsions according to the invention, which is characterized in that the amphiphilic inorganic pigments are dispersed in a manner known per se in the aqueous phase, which, if desired, comprises cosmetic or pharmaceutical auxiliaries, additives and/or active ingredients, with uniform stirring and, where necessary, with heating, and during the homogenization process the preferably liquid fatty phase, which, if desired, likewise comprises cosmetic or pharmaceutical auxiliaries, additives and/or active ingredients, is mixed with the aqueous phase.

The following examples serve to illustrate the present invention, without limiting it. The numerical values in the examples indicate percentages by weight, based on the total weight of the respective preparations.

EXAMPLES

Example 1

Mineral oil	34
caprylic/capric triglyceride	34
TiO_2 (EUSOLEX ® TA)	3
Butylene glycol	3
Water	ad 100

Example 2

Mineral oil	20
Caprylic/capric triglyceride	20
TiO_2 (EUSOLEX ® T2000)	5
Glycerol	3
Butylmethoxydibenzoylmethane	2
Methylbenzylidenecamphor	2
octyltriazone	1
Cetylhydroxyethylcellulose	0.5
Water	ad 100

Example 3

Mineral oil	33
Caprylic/capric triglyceride	33
Glycerol	3
TiO_2 (EUSOLEX ® TA)	2.5
Thickener	2.5
Water	ad 100

Example 4

Caprylic/capric triglyceride	10
Mineral oil	5
TiO_2 (EUSOLEX ® TA)	3
Glycerol	3
Thickener	0.5
Water	ad 100

Example 5

Caprylic/capric triglyceride	66
TiO_2 (KRONOS ® 1171)	5
Glycerol	3
Water	ad 100

Example 6

Caprylic/capric triglyceride	30
Octyl salicylate	5
TiO_2 (KRONOS ® 1171)	3
Glycerol	3
Zinc oxide	2.5
Butylmethoxydibenzoylmethane	2
Methylbenzylidenecamphor	2
Octyltriazone	1
Octyl methoxycinnamate	1
Water	ad 100

Example 7

Caprylic/capric triglyceride	20
Methylbenzylidenecamphor	4
Glycerol	3
Zinc oxide	2.5
Butylmethoxydibenzoylmethane	2
Octyltriazone	2
Thickener	0.5
Water	ad 100

Example 8

Caprylic/capric triglyceride	66
Glycerol	3
TiO_2 (KRONOS ® 1171)	2.5

-continued

Thickener	2.5
Water	ad 100

Example 9

Caprylic/capric triglyceride	22
Mineral oil	11
Zinc oxide	3
Butylene glycol	3
Cetylhydroxyethylcellulose	0.5
Water	ad 100

What is claimed is:

1. An emulsifier-free cosmetic or dermatological preparation, which preparation is a finely dispersed oil-in-water system, said preparation comprising

a) an oil phase;

b) an aqueous phase; and

c) micronized, inorganic pigments particles positioned at an interface of said oil phase and said aqueous phase, said micronized, inorganic pigment particles:

i) have an average particle size of less than 200 nm;

ii) have both hydrophilic and lipophilic properties resulting in an amphiphilic character; and

iii) selected from the group consisting of metal oxides, which are coated on the surface thereof with:

(A) a dimethylpolysiloxane and/or silica gel; and

(B) aluminium hydroxide and/or alumina and/or silicon dioxide; and

d) optionally cosmetic or pharmaceutical auxiliaries, additives and/or active substances.

2. Preparation according to claim 1, wherein the content of the inorganic pigments used is between 0.1% by weight and 30% by weight, based on the total weight of the preparation.

3. Preparation according to claim 1, wherein the particle diameter of the inorganic pigments used is between 5 nm and 100 nm.

4. Preparation according to claim 1, wherein the inorganic pigments used are titanium dioxide and/or zinc oxide.

5. Preparation according to claim 1, wherein the inorganic pigments used have been surface-treated to repel water, the amphiphilic character of the pigments thereby being formed or retained.

6. Preparation according to claim 1, wherein the inorganic pigments used are titanium dioxide particles coated with simethicone and alumina.

7. A process for preparing the emulsifier-free cosmetic or dermatological preparation of claim 1, said process comprising:

a) dispersing an amphiphilic inorganic pigment in an oil phase to form a mixture of said amphiphilic inorganic pigment and said oil phase, said oil phase optionally comprising one or more cosmetic or pharmaceutical auxiliaries, additives and/or active ingredients;

b) homogenizing said mixture by uniform stirring and, optionally, heating; and

c) during said homogenizing, mixing an aqueous phase with said mixture, said aqueous phase also optionally comprising one or more cosmetic or pharmaceutical auxiliaries, additives and/or active ingredients.

8. Preparation according to claim **1**, comprising one or more additives or active ingredients selected from the group consisting of astringents and/or antimicrobial substances.

9. Preparation according to claim **1**, comprising one or more additives or active ingredients selected from the group consisting of antioxidants and/or UV protectants.

10. A method of caring for skin, said method comprising applying to skin a preparation according to any one of claims **1**, **2**, **5**, **6**, **9**, and **8**.

* * * * *

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
DIVISION DE NUEVAS CREACIONES

2020
Bogotá, D.C.,

Abogado:
ALICIA LLOREDA RICAURTE

ASUNTO:	Radicación No.	05 040 025
	Trámite	002
	Evento	001
	Actuación	430
	Oficio	6808
	Folios	018

Como resultado del Examen de Fondo, realizado con fundamento en el artículo 45 de la Decisión 486 de la Comisión de la Comunidad Andina, se comunica:

1. **Documentos estudiados:**

Descripción:	Folios	44 a 69
Reivindicaciones:	Folios	70 a 71
Prioridad:	EP 02256570.9 (2002-10-31)	

2. **Objeto de la Invención**

Titulo de la invención: "Emulsión de agua en aceite que comprende esterolesteres"

Problema Técnico Planteado: cómo mejorar las propiedades organolépticas de la emulsión y aumentar el tamaño de partícula

Solución: Emulsiones agua en aceite que incluyen esteres de ácidos grasos de esterles y ácido fólico

IPC: A23L/130 A23D/700

3. **Reivindicaciones relativas a un uso o a un segundo uso** (Art 14 y 21 D 486)

La Reivindicación 8 no es patentable por que se refiere a un uso.

4. **Determinación del Estado de la Técnica**

El Estado de la Técnica se determinó con base en la fecha de prioridad 2002/10/31 y se encontraron los siguientes documentos que anticipan el objeto de esta solicitud:

Item	Documento	Título	Fecha de Publicación
D1	US 2002/068095	Cholesterol lowering supplement	Jun 6, 2002
D2	US 6440399	Emulsifier-free finely dispersed systems of the water-in-oil type	Ago 27, 2002

5. Análisis de Patentabilidad (Art 14 D486)

Nivel Inventivo (Art18 D486)

Estado de la Técnica más cercano: D1 dado que describe emulsiones tipo agua en aceite que contienen ácido fólico cuya finalidad es disminuir los niveles de colesterol en sangre. (folio 93, párrafos 39 y 41)

Análisis de las diferencias con respecto al estado de la técnica:

Características esenciales de la Solicitud	D1	D2
Emulsión W/O	SI	SI
Ácido fólico	SI	SI
Concentración de 15 ppm a 1%	NO	SI

La presente solicitud reivindica emulsiones de tipo agua en aceite que además comprenden la adición de ácido fólico en una concentración que varía desde 0.0015% hasta 1 %.

La solicitud se diferencia de D1 en la concentración de ácido fólico adicionado a la emulsión que varía desde 15 ppm a 1%.

El Efecto Técnico que logra la diferencia es un mejoramiento de las propiedades organolépticas de la emulsión y del tamaño de partícula obtenido.

El Problema Técnico Objetivo sería cómo mejorar las propiedades organolépticas de la emulsión y aumentar el tamaño de partícula.

D2 describe la formulación de emulsiones de tipo agua en aceite utilizando como antioxidantes el ácido fólico y sus derivados a concentraciones que abarcan desde 0.001% hasta 30%. (Folio 100, columna 6, líneas 41 a 46)

Para el experto en la materia sería obvio incluir las concentraciones de D2 en la formulación de la emulsión de D1, para lograr resolver el problema técnico.

Las reivindicaciones 2 a 6 no mencionan características técnicas que hagan inventiva la composición.

La reivindicación 7, relacionada con el método de preparación de una emulsión agua en aceite, no enseña características del mismo que lo hagan inventivo sobre la materia descrita por D2.

6. Conclusión

Los requisitos de Patentabilidad de la presente Solicitud se encuentran afectados así:

N°	Documento	Reivindicaciones afectadas	Requisito que afecta
D1	US 2002/068095	1-6	Nivel Inventivo
D2	US 6440399	1-6	Nivel Inventivo

En cumplimiento del artículo 45 de la Decisión 486 de la Comisión de la Comunidad Andina, se le indica que debe dar respuesta dentro del término de 60 días contados a partir de la fecha de notificación de la presente comunicación. En caso de no dar respuesta al presente requerimiento, o si a pesar de la respuesta subsistieran los impedimentos para la concesión, se denegará la patente.

Notifíquese el presente oficio conforme a lo dispuesto en el numeral 5.2, literal e), del capítulo quinto del título primero de la Circular Única N° 10 de 2001.

ALIX CARMENZA CÉSPEDES DE VERGEL
Jefe de División de Nuevas Creaciones

El anterior requerimiento fue notificado por fijación en lista, de fecha 12 JUN. 2009

CONCEPTO TECNICO No. 1898	EXAMINADOR TÉCNICO Código: 202092