Note: Within nine months of the publication of the mention of the grant of the European patent in the European Patent Bulletin, any person may give notice to the European Patent Office of opposition to that patent, in accordance with the Implementing Regulations. Notice of opposition shall not be deemed to have been filed until the opposition fee has been paid. (Art. 99(1) European Patent Convention).
The present disclosure relates compositions that contain bimetal complexes. The bimetal complexes can be prepared by reacting a polyfunctional compound with two or more coordination elements.

Polycarboxylic acids are polyfunctional acids used in many products. The ion form of carboxylic acids, as well as its esters and salts, are known as carboxylates. Various copper carboxylates are known through the extensive use of the carboxylate ion in crystal engineering to explore the structural chemistry of copper (II) carboxylates, which exist, for example as copper (II) malonates, copper (II) copper glutamates, copper citrates and other copper complexes known. However, the study of copper (II) reaction products of polyfunctional acids and the formation of carboxylates are problematic in that the conditions of synthesis, stoichiometry and temperature should be known and applied in order to synthesize the desired product. For example, the mixture of copper carbonate and malonic acid in a 1:2 molar ratio kept at 5°C for weeks results in the formation of deep blue copper (II) malonate trihydrate crystals.

It would be desirable to provide compositions containing reaction products of polyfunctional carboxylic acid compounds with two or more coordination elements. For example, it would be desirable to provide malonates having both copper and at least one other metallic constituent, such as zinc. These can be obtained by reacting a mixture of malonic and a 3:1:1 molar ratio with the metallic components resulting in the formation of greenish-blue copper II zinc II malonate crystals.

Polyamines are polyfunctional bases used in many products. When combined with metallic constituent, the ion form of amines as well as their amides and salts, can produce amino complexes. Various copper amine complexes are used extensively in crystal engineering to explore the structural chemistry of amine complexes, such as, for example, copper (II) amine complexes. Copper (II) amine complexes exist in numerous forms, many of which have an intense blue color. For example, intense blue various copper (II) ethylenediamine complexes are known.

However, the study of reaction products of poly-functional amines and the formation of amine complexes are problematic in that conditions of synthesis, stoichiometry and temperature should be known and applied in order to synthesize the desired product. For example, a mixture of butylene diamine, copper chloride, zinc chloride in a 3:1:1 molar ratio results in the formation of dry, blue crystals.

It would be desirable to provide compositions containing reaction products of polyfunctional amine compounds with two or more coordination elements. For example, it would be desirable to provide amines complexes having both copper and at least one other metallic constituent, such as zinc.

Poly-functional organic compounds having a carboxyl group and an amine group are known as amino acids. The ionic form of amino acids vary with the pH of the media, with ionic forms of the acid being known as carboxylates and the ionic forms of the amine as being known as ammonium complexes. Various copper amino acid complexes are known through the extensive use of the amino acids in crystal engineering to explore the structural chemistry of copper (II) amino acid complexes. They exist in numerous forms such as copper (II) glycinate, copper II glutamate, etc. However, one study of reaction products of polyfunctional amino acids and the formation of amino acid complex is problematic in that conditions of synthesis, stoichiometry and temperature should be known and applied in order to synthesize the desired product.

It would also be desirable to provide compositions containing reaction products of amino acid compounds with two or more coordination elements. For example, it would be also desirable to provide amino acid complexes having copper and at least one other metallic constituent, such as zinc. For example in a mixture of glutamic acid, zinc carbonate and copper carbonate in a 3:1:1 molar ratio results in the formation of greenish-blue crystals. It would be desirable to provide compositions containing reaction products of polyfunctional compounds with two or more coordination elements. It would also be desirable to provide glutamates having both copper and at least one other metallic constituent, such as zinc.

Further relevant background is constituted by the following documents. Huang et al., Zhongnan Minzu Daxue Xuebao, Ziran Kexueban (2004), 23 (3), 12 to 16 discloses a study on the thermal decomposition process and kinetics of copper zinc oxalates. WO 94/15216 A1 discloses the use of a copolymer of and a derivative salt of a variable valency metal with unsaturated carboxylic acid or sodium silicate. US 2003/0059484 A1 discloses an agent for a cosmetic composition which is a divalent metal salt or complex, such as, in particular, a magnesium aspartate or magnesium chloride.
SUMMARY

[0012] Compositions in accordance with the present disclosure contain a bimetal complex. The bimetal complex can be the reaction product of a polyfunctional compound with two or more coordination elements. The polyfunctional compound can be, for example, a dicarboxylic acid or an amino acid. The coordination elements are copper and zinc.

[0013] Methods of making such reaction products are also described. In embodiments, bimetal complexes are made by 1) contacting one or more polyfunctional compounds with two or more coordination elements, wherein the molar ratio of polyfunctional compound to two or more coordination elements is at least 3:2; and 2) isolating the reaction product.

[0014] In embodiments, copper-zinc malonate complexes are synthesized from malonic acid and copper and zinc constituents. Methods of making copper-zinc dual salts are also described. In embodiments, copper-zinc malonate compositions are made by:

1) contacting malonic acid with one or more bases containing copper and zinc constituents in an aqueous solution, wherein the molar ratio of malonic acid to copper to zinc is about 3:1:1; and
2) recovering the copper-zinc malonate product.

[0015] Excess malonic acid in the manufacturing process may drive the formation of copper-zinc malonates which precipitate in the reaction solution.

DETAILED DESCRIPTION OF PREFERRED EMBODIMENTS

[0016] The preparation of reaction products of polyfunctional compounds with two or more coordination elements and compositions containing such reaction products are described.

[0017] The polyfunctional compound can be a dicarboxylic acid, a diamine or an amino acid. It should of course be understood that mixtures of polyfunctional compounds may be used.

[0018] Non-limiting examples of dicarboxylic acids include maleic acid, fumaric acid, citraconic acid, itaconic acid, glutaric acid, phthalic acid, isophthalic acid, cyclohexane dicarboxylic acid, succinic acid, adipic acid, sebacic acid, azelaic acid, malonic acid, dodecanedioic acid, 1,18-octadecanedioic acid, dimer acids (prepared from a mono-, di- or triunsaturated fatty acid, acid wax, acid anhydride grafted wax, or other suitable polyfunctional acid reacting compound), alkenyl succinic acids (such as n-dodecylsuccinic acid, docecylcucinic acid and octadecenylsuccinic acid). The dicarboxylic acid can be present in acidic form, anhydride form, salt form, or mixtures thereof.

[0019] Amino acids may also be used as the polyfunctional compound. Amino acids are known to those skilled in the art and include at least a carboxylic acid functionality and an amino functionality. Suitable amino acids include naturally occurring amino acids and synthetic amino acids. Examples of amino acids include: glycine; aminopolycarboxylic acids (e.g., aspartic acid, β-hydroxyaspartic acid, glutamic acid, β-hydroxyglutamic acid, β-methylaspartic acid, β-methylglutamic acid, β,β-dimethylaspartic acid, γ-hydroxyglutamic acid, β,γ-dihydroxyglutamic acid, β-phenylglutamic acid, γ-methyleneglutamic acid, 3-aminoacidic acid, 2-aminopimelic acid, 2-aminoisobutyric acid, and 2-aminoisobutyric acid); amino acid amides such as glutamine and asparagine; polyamino- or polybasic-monocarboxylic acids such as arginine, lysine, β-aminobutyamine, γ-aminobutyamine, ornithine, citruline, homoarginine, homocitruline, hydroxylsine, allohydroxylsine and dianmino acid acid; other basic amino acid residues such as histidine; diaminodicarboxylic acids such as α,α'-diaminosuccinic acid, α,α'-diaminodiacid acid, α,α'-diaminopimelic acid, α,α'-diaminoacid acid, α,α'-diaminoadipic acid, α,α'-diaminoadipic acid, α,α'-diaminobutyric acid, α,α'-diaminoocylacetic acid, and α,α'-diaminosebacic acid; imino acids such as proline, hydroxyproline, alloxaproline, γ-methylproline, piperocic acid, 5-hydroxyproepic acid, and azetidine-2-carboxylic acid; mono- or dialkyl (typically C₃-C₆ branched or normal) amino acids such as alanine, valine, leucine, allylglycine, butyrie, norvaline, norleucine, heptlyne, α-methylserine, α-amino-α-methyl-γ-hydroxyvaleric acid, α-amino-α-methyl-δ-hydroxyvaleric acid, α-amino-α-methyl-ε-hydroxyacaproic acid, isovaline, α-methylglutamic acid, α-aminoisobutyric acid, α-aminoethylactic acid, α-aminoisopropylacetic acid, α-aminoisopropylacetic acid, α-amino-isopropylacetic acid, α-amino-isopropylacetic acid, α-amino-isopropylacetic acid, α-amino-isopropylacetic acid, α-aminoisoyamatic acid, α-methylaspartic acid, α-methylglutamic acid, 1-aminoisocytopropane-1-carboxylic acid, isoleucine, alloisoleucine, tert-leucine, β-methyltrytophan and α-amino-β-ethyl-β-phenylpropionic acid; β-phosalenri; aliphatic α-amino-β-hydroxy acids such as serine, β-hydroxyisicadine, β-hydroxyisicadine, β-hydroxyisicadine, and α-amino-β-hydroxysteaeric acid; α-Amino, α, α, γ, δ or ε-hydrox acids such as homoserine, γ-hydroxyvaline, δ-hydroxyvaline and epsilon-hydroxyvaline residues; canavine and canavine; γ-hydroxymothamine; 2-hexosaminic acids such as D-glucosaminic acid or D-galactosaminic acid; α-Amino-β-thiols such as penicillamine, β-thiornorvaline or β-thiornorvaline; other sulfur containing amino acid residues including cysteine; homocysteine, β-phenylmethylionine, methione, S-ally-a-cysteine sulfoxide, 2-thihostidine, cystathionine, and thiol ethers of cysteine or homocysteine; phenylalanine, trytophan and ring-substituted α amino acids such as the phenyl- or cyclohexylaminos α-aminophenylacetic acid, aminocyclohexylactic acid and α-aminophenolpropionic acid; phenylalanine analogues and derivatives.
comprising aryl, lower alkyl, hydroxy, guanidino, oxalkylether, nitro, sulfur or halo-substituted phenyl (e.g., tyrosine, methylyrosine and o-chloro-, p-chloro-, 3,4-dichloro-, m- or p-methyl-, 2,4,6-trimethyl-, 2-ethoxy-5-nitro-, 2-hydroxy-5-nitro- and p-nitrophenylalanine); furl-, thienyl-, pyridyl-, pyrimidinyl-, purinyl- or napththalenines; and tryptophan analogues and derivatives including kynurenine, 3-hydroxykynurenine, 2-hydroxytryptophan and 4-carboxytryptophan; α-
Amino substituted amino acids including sarcosine (N-methylglycine), N-benzylglycine, N-methylalanine, N-benzylalanine, N-methylphenylalanine, N-benzylphenylalanine, N-methylyvaline and N-benzylvaline; and α-Hydroxy and substituted α-hydroxy amino acids including serine, threonine, allothreonine, phosphoserine and phosphothreonine. glycine, alanine, valine, leucine, isoleucine, serine, threonine, cysteine, methionine, glutamic acid, aspartic acid, lysine, hydroxysine, arginine, histidine, phenylalanine, tyrosine, tryptophan, proline, asparagine, glutamine and hydroxyproline. Amine polycarboxylic acids, e.g., aspartic acid, β-hydroxyaspartic acid, glutamic acid, β-hydroxyglutamic acid, β-methylaspartic acid, β-methylglutamic acid, β,β-dimethylaspartic acid, γ-hydroxyglutamic acid, β,γ-dihydroxyglutamic acid, β-phenylglutamic acid, γ-methyleneglutamic acid, 3-aminoacidic acid, 2-aminopimelic acid and 2-aminosebacic acid. Polyaminoacids may also be used provided they form complexes with the coordination elements employed.

[0020] The polyfunctional compound is reacted with copper and zinc.

[0021] For example, water soluble salts containing the coordination element may be used. The salts may be organic or inorganic. Suitable water-soluble copper salts include copper sulfate, fluoroborate, hydroxide, borate, fluoride, carbonate, oxochloride, formate or acetate. Suitable water-soluble zinc salts include zinc chloride, zinc bromide, zinc iodide, zinc chloride, zinc bromate, zinc chlorate, zinc sulfate, zinc nitrate, zinc nitrite, zinc borate, zinc carbonate, basic zinc borate, zinc hexаfluorosilicate, zinc hypophosphate, zinc glycerophosphate, zinc bichromate, zinc citrate, zinc thionate, zinc dithionate, zinc tetraheptonate, zinc thiocyanate, zinc benzoate, zinc acetate, zinc salicylate, zinc picrate, zinc permanganate, zinc hydrogen phosphate, zinc formate, zinc ethylsulfate and zinc phenolsulfonate. Examples of suitable water soluble nickel salts that may be used include nickel sulfate hexahydrate and nickel chloride hexahydrate.

[0022] For carrying out the process, a reaction solution can be prepared by mixing the various ingredients in water. Water in the mixture may advantageously be added in limited amounts sufficient to allow the reaction product to precipitate from solution upon formation. Accordingly, the reaction mixture is not so dilute as to prevent product precipitate formation. Where necessary, mixing and heating can be used to bring the reactants to 40 - 100°C in order to solubilize the reactants. As a result, reactant solubility may be enhanced through energy input such as microwave heating or addition of boiling water. The input of the energy may take place through any instrument capable of heating the aqueous reaction mixture. The reaction products formed in solution may be immediately separated so that their production can take place in a continuous process. Where a short reaction time and rapid crystallization of the reaction product occur, the conversion may be carried out continuously, and the recovery of the resultant solid product may take place by any conventional manner such as filtering, centrifugation, or sedimentation.

[0023] The polyfunctional compound is present in the reaction mixture in amounts that will contact metal cations in an aqueous solution. Suitable amounts of polyfunctional compound also include excess amounts in relation to the amount of a second type to a central unit by ionic bonds. For example, the reaction product may be in the form of a trinuclear ion, where structurally independent coordination element hydrates are bridged by a central unit. However, various coordination modes are possible depending on the source of the coordination elements and synthesis conditions. In embodiments, the central unit may be a multi-membered ring such as eight-membered ring, six-membered ring, and four-membered metalacycle for bridging or chelating functions between the coordination element constituents. Accordingly, the crystal structures of the reaction products can be very diverse, from ionic to three-dimensional polymers. In embodiments, the reaction products are present in several hydrate, and polymorphic forms.

[0024] In embodiments, the coordination elements may be present as one or more ionic compounds formed by joining one or more independent coordination element molecules or ions of a first type and coordination element molecules or ions of a second type to a central unit by ionic bonds. For example, the reaction product may be in the form of a trinuclear cation, where structurally independent coordination element hydrates are bridged by a central unit. However, various coordination modes are possible depending on the source of the coordination elements and synthesis conditions. In embodiments, the central unit may be a multi-membered ring such as eight-membered ring, six-membered ring, and four-membered metalacycle for bridging or chelating functions between the coordination element constituents. Accordingly, the crystal structures of the reaction products can be very diverse, from ionic to three-dimensional polymers. In embodiments, the reaction products are present in several hydrate, and polymorphic forms.

[0025] In embodiments, suitable reaction products can be non-toxic bimetal complexes that include copper, and zinc, constituents. Such copper, and zinc, reaction products include, but are not limited to water soluble compounds that contain copper, and zinc. Non-limiting examples of water-soluble bimetal complexes include copper-zinc citrate, copper-zinc oxalate, copper-zinc tartarate, copper-zinc malate, copper-zinc succinate, copper-zinc malonate, copper-zinc maleate, copper-zinc aspartate, copper-zinc glutamate, copper-zinc glutarate, copper-zinc fumarate, copper-zinc glutarate, copper-zinc polyacrylic acid, and combinations thereof. In embodiments, copper, and zinc, salts of organic dicarboxylic acids are suitable for use in accordance with the present disclosure. In embodiments, suitable salts can be doped such that the unit cell of the salt has zinc constituents dispersed therein. Such zinc constituents may either
Malonic acid refers to 1,3-propanedioic acid, a dicarboxylic acid with structure CH$_2$(COOH)$_2$ or:

Due to the short reaction time and the rapid crystallization of the copper-zinc constituents, the reaction can take place in a continuous process. The total concentration of product formed in the reaction mixture may exceed the solubility limit, and the unit cell of the salt has zinc constituents dispersed therein.

In embodiments, copper and zinc constituents may either substitute a copper constituent or fill a preexisting void in the unit cell.

Cu/Zn Malonate Preferred Embodiments

In embodiments, malonic acid may be reacted with salts containing copper and zinc constituents in an aqueous solution. One or more bases of copper and zinc, and water. In an aqueous reaction solution, suitable salt forms provide copper and zinc cations capable of bonding to malonate anions. Other suitable ingredients for the formation of copper-zinc malonates will include the replacement of bases of copper and zinc with the metallic form of copper and zinc. The elemental form of copper and zinc are known as copper and zinc metals and will be dissolved in the acidic water media as they react with malonic acid.

Suitable copper salts can be doped such that the unit cell of the salt has zinc constituents dispersed therein. Such zinc constituents may either substitute a copper constituent or fill a preexisting void in the unit cell.

The ion form of malonic acid, as well as its esters and salts, are known as malonates. For example, diethyl malonate is ethyl ester of malonic acid. As used herein, the term copper-zinc malonate applies to any salt substances formed from malonic acid having copper and zinc constituents.

Suitable ingredients for the formation of copper-zinc malonates include malonic acid, one or more bases of copper and zinc, and water. In an aqueous reaction solution, suitable salt forms provide copper and zinc cations capable of bonding to malonate anions. Other suitable ingredients for the formation of copper-zinc malonates will include the replacement of bases of copper and zinc with the metallic form of copper and zinc. The elemental form of copper and zinc are known as copper and zinc metals and will be dissolved in the acidic water media as they react with malonic acid.

One or more salts containing copper and zinc constituents are present in amounts that will contact malonic acid in an aqueous solution. Suitable salts for making copper-zinc malonate compositions in accordance with this disclosure include metal salts containing complex-forming metal ions of copper and/or zinc. Non-limiting examples of suitable metal salts are copper (I) and (II) salts such as copper chloride, copper bromide, copper fluoride, copper nitrate, copper fluoroborate, copper sulfate, copper acetate, copper trifluoroacetate, copper stearate, copper octoate, copper methacrylate, copper malonate, copper benzoate; zinc salts such as zinc bromide, zinc chromate, zinc chloride, zinc stearate, zinc octoate, and zinc ethylhexoate. In embodiments, the aqueous solution may include one or more metallic salts, such as cupric carbonate (CuCO$_3$Cu(OH)$_2$), zinc carbonate (3Zn(OH)$_2$·2ZnCO$_3$), metallic copper, metallic zinc and combinations thereof. Basic salts such as basic zinc salts, basic copper salts, and combinations thereof are also suitable for use in accordance with the present disclosure. In embodiments, suitable metal basic salts are: copper (I) and (II) salts such as copper carbonate, copper oxide, and copper hydroxide; and zinc salts such as zinc carbonate, zinc oxide, and zinc hydroxide.

For carrying out the process, the reaction solution can be prepared by mixing the various ingredients in water where malonic acid and the salts may ionize and become more reactive. Water in the mixture is added in limited amounts sufficient to allow copper-zinc malonates to precipitate from solution upon formation. Accordingly, the reaction mixture is not so dilute as to prevent product precipitate formation.

Where copper and zinc salts in the reaction mixture are insoluble and form dispersions (such as at cooler temperatures), mixing and heating steps can be applied to bring the reactants to 40 - 100°C in order to solubilize the reactants. As a result, reactant solubility may be enhanced through energy input such as microwave heating or addition of boiling water dissolver. The input of the energy may take place through any instrument capable of heating the aqueous reaction mixture. The copper-zinc malonate complexes formed in solution may be immediately separated so that their production can take place in a continuous process. Due to the short reaction time and the rapid crystallization of the copper-zinc malonate product, the conversion may be carried out continuously, and the recovery of the resultant solid product may take place by any conventional manner such as filtering, centrifugation, or sedimentation.

In the production of the reaction mixture, the concentration of the polyfunctional compound and that of the copper and zinc constituents may be pre-selected so that the total concentration of product formed exceeds the solubility
equilibrium. This will result in product precipitating from solution in solid form for easy collection.

In embodiments, the final composition may be a deep blue crystal having good yield and substantial crystalline purity. Suitable copper-zinc malonate forms in accordance with the present disclosure include any salt formed from the neutralization of malonic acid by one or more copper containing molecules and one or more zinc containing molecules. Illustrative examples include salt formed by the neutralization of malonic acid by cupric carbonate (CuCO$_3$·Cu(OH)$_2$), and zinc carbonate (3Zn(OH)$_2$·ZnCO$_3$) in an aqueous solution. Here copper may be added first, followed by zinc in order to obtain the salts of the present disclosure.

In embodiments, the copper-zinc malonates may be one or more ionic compounds formed by joining one or more independent copper molecules or ions and one or more independent zinc molecules or ions to a central unit by ionic bonds. For example, the copper-zinc malonate may be in the form of a trinuclear cation, where structurally independent copper and zinc hydrates are bridged by a central unit such as an octahedral diaquadimalonatocopper (II) unit. However, various coordination modes are possible depending on the source of the copper and zinc and synthesis conditions. In embodiments, the central unit malonate ion may be a multi-membered ring such as eight-membered ring, six-membered ring, and four-membered metalocycle for bridging or chelating functions between the copper and zinc constituents. Accordingly, the crystal structures of copper-zinc malonates can be very diverse, from ionic to three-dimensional polymers. In embodiments, the copper-zinc malonates can be found in several hydrate, and polymorphic forms.

In embodiments, the process parameters are especially advantageous if the polyfunctional compound is added to excess in comparison to the metal counter cation constituents. Depending on the desired complex, the latter are added so that the molar ratio of polyfunctional compound to metal ions is approximately 3:2.

Embodiments of Compositions Containing the Reaction Products

In embodiments, the resulting reaction products may serve as active ingredients in compositions suitable for contact with a subject. Such active ingredients may be combined with numerous ingredients to form products of numerous chemical applications, such as catalytical agents, crosslinking of polymers, superconducting electrical materials, pharmaceutical drugs, food supplements, etc. The active ingredients in suitable toxicological compositions can be applied to the skin, or other tissues of humans or other mammals. Such products may include a dermatologically or pharmacologically acceptable carrier, vehicle or medium, for example, a carrier, vehicle or medium that is compatible with the tissues to which they will be applied. The term "dermatologically or pharmaceutically acceptable," as used herein, means that the compositions or components thereof so described are suitable for use in contact with these tissues or for use in patients in general without undue toxicity, incompatibility, instability, allergic response, and the like. In embodiments, compositions in accordance with the present disclosure can contain any ingredient conventionally used in cosmetics and/or dermatology. In embodiments, active ingredients may be formulated to provide crystals in solution, as well as solid forms.

In embodiments, products containing a reaction product in accordance with the present disclosure as an active ingredient can be in the form of solutions, emulsions (including microemulsions), suspensions, creams, lotions, gels, powders, or other typical solid or liquid compositions used for treatment of age related skin conditions. Such compositions may contain, in addition to the reaction product in accordance with this disclosure, other ingredients typically used in such products, such as antimicrobials, moisturizers and hydration agents, penetration agents, preservatives, emulsifiers, natural or synthetic oils, solvents, surfactants, detergents, gelling agents, emollients, antioxidants, fragrances, fillers, thickeners, waxes, odor absorbers, dyestuffs, coloring agents, powders, viscosity-controlling agents and water, and optionally including anesthetics, anti-itch actives, botanical extracts, conditioning agents, darkening or lightening agents, glitter, humectants, mica, minerals, polyphenols, silicones or derivatives thereof, sunblocks, vitamins, and phytomedicinals.

As an illustrative example, products can be formulated to contain copper-zinc malonate in amounts from about 0.001 to about 5 % by weight of the total composition. In embodiments, products can be formulated to contain copper-zinc malonate in an amount from about 0.05 to about 1.0 % by weight of the total composition. In other embodiments, the amount of copper-zinc malonate is from about 0.1 to about 5 % by weight of the total composition. Here, the copper-zinc malonate present may be in a pharmaceutically acceptable salt form. Other active ingredients may be provided in the formulations at the same concentrations.

In embodiments, compositions in accordance with the present disclosure can be topically applied to skin in need of improvement such as the reduction or elimination of an undesirable dermatological condition. As used herein the word "treat," "treating" or "treatment" refers to using the actives or compositions of the present disclosure prophylactically to prevent outbreaks of undesirable dermatological conditions, or therapeutically to ameliorate an existing dermatological condition, and/or extend the duration of the aesthetic benefit of a skin procedure. A number of different treatments are now possible, which reduce and/or eliminate undesirable skin conditions.

As used herein "undesirable skin condition" refers to any skin condition that may require treatment of any sort,
including skin having one or more undesirable appearances and/or disagreeable tactile sensations. The term further refers to any cosmetically undesirable skin condition, as well as any undesirable diseased or damaged skin condition.

**[0042]** Non-limiting examples of undesirable skin conditions which can be treated with the topical application of compositions in accordance with the present disclosure include: acne vulgaris (pimples); atopie dermatitis; birthmarks; cafe-au-lait spots; common benign skin tumors or growths; common diseases of the nail such as nail infections caused by bacteria, fungi, yeast and/or virus; paronychia; nail disorder due to skin disease such as psoriasis, and/or nail injury; common skin conditions around the eyes such as eyelid contact dermatitis, atopic dermatitis, bacterial skin infection (impetigo or conjunctivitis), xanthelasma, syringoma, skin tags, milia, Naevus, and/or portwine stains; common skin condition associated with housework such as irritant contact dermatitis, allergic contact dermatitis, contact urticaria, fungal infections, paronychia, and/or viral warts; common diseases of the scalp such as seborrheic dermatitis, psoriasis of the scalp, lichen planus, discoid lupus erythematosus (DLE), alopecia areata, seborrheic keratoses (seborrheic warts, age spots), solar keratoses, angiosarcoma, fungal infection (ringworm, tinea Capitis), bacteria infections of the hair follicles (folliculitis, boils), and/or shingles (Herpes Zoster); common diseases in children such as atopic dermatitis, atopic eczema, discoid eczema, pityriasis alba, vitiligo, and/or alopecia areata; common diseases of the mouth and lips such as oral candidiasis, oral leukoplakia, aphthous ulcers, and/or oral lichen planus; common skin problems in elderly such as appearance and texture changes, senile purpura, xerosis /asteatotic eczema, skin Infections /infestations, pigmentary changes, blistering disorders, non-cancerous skin growths, cancerous skin growths, adverse drug reaction, and/or stasis dermatitis; common viral warts; contact allergy; diaper candidiasis, drug allergy, folliculitis; freckles; fungal infections of the skin such as white spot, athlete’s foot, jock itch, and/or moniliais/candidiasis; guttate hypomelanosis; hair loss; hand eczema; impetigo; lines, crow’s feet, wrinkles, etc.; melanoma; molluscum contagiosum; occupational skin disease such as irritation and/or allergy; post-Inflammatory pigmentation; psoriasis; rosacea; shingles; skin cancers; skin diseases in diabetes mellitus; skin diseases in pregnancy; skin disorders caused by cosmetics such as irritant contact dermatitis and/or allergic contact dermatitis; cosmetic induced pimples (acne), sunscreens allergy, and/or special cosmetic allergies, solar lentigines; tinea capitis; viral warts; vitiligo; and combinations of these undesirable skin conditions.

**[0043]** In embodiments, compositions in accordance with the present disclosure are suitable for treating diseased skin, or any condition which can result from the excessive amount of pathogens such as fungi, viruses, and or bacterium affecting the skin in any way.

**[0044]** In embodiments, an undesirable skin condition is skin that has a rough texture or uneven appearance such as psoriasis, bumps, razor burns, and/or patches.

**[0045]** The particular active ingredient or ingredients employed, and the concentration in the compositions, generally depends on the purpose for which the composition is to be applied. For example, the dosage and frequency of application can vary depending upon the type and severity of the skin condition.

**[0046]** Treatments in accordance with the present disclosure contact skin with one or more active ingredients such as those containing copper, zinc and/or silver in an effective amount to improve the undesirable skin conditions. In embodiments, patients are treated by topically applying to skin suffering a condition, one or more copper-zinc malonates. In embodiments, patients are treated by topically applying to skin suffering from a condition, one or more salts in accordance with the present disclosure. The active ingredient is applied until the treatment goals are obtained. However, the duration of the treatment can vary depending on the severity of the condition. For example, treatments can last several weeks to months depending on whether the goal of treatment is to reduce or eliminate the skin condition.

**[0047]** In treatment embodiments, the compositions and methods in accordance with the present disclosure can be combined with other skin treatment systems. For example, the bimetallic salt complexes and be applied to skin in combination with skin treatment systems such as the Obagi NuDerm® skin treatment system and related Obagi skin care products from O.M.P. Inc. of Long Beach California. More specifically copper-zinc malonate compositions can be combined with the Obagi NuDerm® skin treatment system in order to promote the beneficial affects of that system. The active ingredients and formulations in accordance with the present disclosure may either be incorporated into other product formulations, or applied to the skin before, after, and/or during other skin treatments.

**[0048]** In embodiments, the compositions may contain any active ingredient or be formulated and applied as described in commonly owned U.S. Patent Application entitled Anti-aging Treatment Using Copper-Zinc Compositions (U.S. Serial No. 11/452,642 filed June 14, 2006).

**[0049]** The following examples further illustrate compositions and methods in accordance with this disclosure.

Example 1

**[0050]** Example 1 below shows suitable ingredients of a reaction mixture for forming copper-zinc malonates in accordance with the present disclosure.
Example 2

1.8 g of malonic acid (CH₂(COOH)₂) was combined with 0.632 grams of cupric carbonate (CuCO₃Cu(OH)₂), 0.626 g of zinc carbonate (3Zn(OH)₂ZnCO₃), and 100 ml of water to form a dispersion. The solution was heated until the reactants went into solution. Well-defined deep-blue crystals precipitated and were separated from the aqueous solution of malonic acid, cupric carbonate, and zinc carbonate (3:1:1 molar ratio) that had been kept at room temperature. Dual salt was formed by replacing acid groups with copper and zinc cations in the same molecule. The deep blue crystals were found to have a melting point of about 210°C.

Example 3

1.8 g of malonic acid (CH₂(COOH)₂) was combined with 0.632 grams of cupric carbonate (CuCO₃Cu(OH)₂), 0.626 g of zinc carbonate (3Zn(OH)₂ZnCO₃), and 100 ml of boiling water. Well-defined deep-blue crystals were separated from the aqueous solution of malonic acid, cupric carbonate, and zinc carbonate (3:1:1 molar ratio) that had been kept at room temperature for 1 week.

Example 4

3 moles of malonic acid is thoroughly mixed with 1 mole of copper as cupric carbonate and 1 mole of zinc as zinc carbonate in a stirred tank reactor containing 100 ml of heated water (approximately 95-100°C). After a short reaction time, copper-zinc malonate precipitates out of solution with a high yield. A filtration step is used to isolate the complex as a powder. Deep blue crystals are obtained having a melting point of about 210°C.

Example 5

In embodiments, copper-zinc malonate formulations have the following make-up:

<table>
<thead>
<tr>
<th>COMPONENT</th>
<th>% BY WEIGHT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Copper-zinc malonate* (Active ingredient)</td>
<td>0.1 %</td>
</tr>
<tr>
<td>Glycerine</td>
<td>3.0%</td>
</tr>
<tr>
<td>Propylene Glycol</td>
<td>25.0%</td>
</tr>
<tr>
<td>Distilled Water</td>
<td>71.9%</td>
</tr>
</tbody>
</table>

Example 6

A 72 year old woman is suffering from wrinkling on her face. The composition of example 5 suitable for treatment of skin containing an effective amount of copper-zinc malonate active ingredient is routinely applied to her face twice daily. Wrinkling is reduced or eliminated.

Example 7

3 moles of glutamic acid is thoroughly mixed with 1 mole of copper as cupric carbonate and 1 mole of zinc as zinc carbonate in a stirred tank reactor containing 100 ml of heated water (approximately 95-100°C). After a short reaction
time, copper-zinc glutamate precipitates out of solution with a high yield. A filtration step is used to isolate the complex
as a powder.

Claims

1. A method of forming a bimetal complex comprising
dissolving a polyfunctional component selected from the group consisting of dicarboxylic acids, diamines and
amino acids in a solvent to form a solution;
adding a source of a first coordination element to the solution;
adding a source of a second coordination element to the solution; and
recovering a bimetal complex,
wherein the coordination first and second elements are copper and zinc, respectively.

2. A method as in claim 1 wherein the polyfunctional component is selected from the group consisting of maleic acid,
fumaric acid, citraconic acid, itaconic acid, glutaric acid, phthalic acid, isophthalic acid, terephthalic acid, cyc-
clohexane dicarboxylic acid, succinic acid, adipic acid, sebacic acid, azelaic acid, malonic acid, dodecanedioic acid,
1,18-octadecanedioic acid, dimer acids and alkenyl succinic acids, and is preferably malonic acid.

3. A method as in claim 1 wherein the source of a first coordination element provides Cu²⁺ ions in the solution, preferably
cupric carbonate.

4. A method as in claim 1 wherein the source of a second coordination element provides Zn²⁺ ions in the solution, preferably
zinc carbonate.

5. A method as in claim 1 wherein the polyfunctional component, copper and zinc are added to the solution in a molar
ratio of polyfunctional component to copper and zinc of at least 3:2.

6. A method of formulating a product incorporating forming a bimetal complex as described in claim 1 and further
comprising combining the bimetal complex thus obtained with a pharmaceutically or dermatologically acceptable
carrier.

7. A method as in claim 6 further comprising including in the product one or more members selected from the group
antimicrobials, moisturizers and hydration agents, penetration agents, preservatives, emulsifiers, natural or synthetic
oils, solvents, surfactants, detergents, gelling agents, emollients, antioxidants, fragrances, fillers, thickeners, waxes,
odor absorbers, dyestuffs, coloring agents, powders, viscosity-controlling agents and water, and optionally including
anesthetics, anti-itch actives, botanical extracts, conditioning agents, darkening or lightening agents, glitter, humect-
ants, mica, minerals, polyphenols, silicones or derivatives thereof, sunblocks, vitamins, and phytomedicinals.

8. A method as in claim 6 wherein the bimetal complex is added to the product in an amount of from between 0.001
to 5 % by weight of the total product.

9. A composition comprising:
a dermatologically or pharmaceutically acceptable carrier;
one or more copper molecules;
one or more zinc molecules; and
a central unit,
wherein the central unit comprises at least one polyfunctional compound selected from dicarboxylic acids, diamines,
and amino acids and the center unit bridges the one or more copper molecules and one or more zinc molecules
by coordinate bonding.

10. A composition as in claim 9 wherein the central unit comprises at least one polyfunctional compound selected from
the group selected from dicarboxylic amino acids.
11. A malonate composition comprising:

one or more copper molecules;
one or more zinc molecules; and
a malonate central unit,

wherein the malonate central unit bridges the one or more copper molecules and one or more zinc molecules by coordinate bonding.

12. The malonate composition of claim 11 wherein the one or more copper molecules is a tetraaquacopper (II) square.

13. The malonate composition of claim 11 wherein the one or more zinc molecules is a tetraaquazinc square.

14. The malonate composition of claim 11 wherein the central unit is an octahedral diaquadimalonatocopper (II) unit.

15. A composition as in claim 9 wherein the central unit comprises a plurality of amino acids.

Patentansprüche

1. Verfahren zum Bilden eines Bimetallkomplexes, welches umfasst:

   Auflösen einer polyfunktionellen Komponente gewählt aus der Gruppe bestehend aus Dicarbonsäuren, Diaminen und Aminosäuren in einem Lösungsmittel, um eine Lösung zu bilden;
   Zugeben einer Quelle eines ersten Koordinationselements zu der Lösung;
   Zugeben einer Quelle eines zweiten Koordinationselements zu der Lösung; und
   Gewinnen eines Bimetallkomplexes,
   wobei die ersten und zweiten Elemente der Koordination Kupfer bzw. Zink sind.

2. Verfahren nach Anspruch 1, wobei die polyfunktionelle Komponente gewählt wird aus der Gruppe bestehend aus Maleinsäure, Fumarsäure, Citraconsäure, Itacon säure, Glutaconsäure, Phthalsäure, Isophthalsäure, Terephthalsäure, Cyclohexandicarbonsäure, Bernsteinsäure, Adipinsäure, Sebacinsäure, Azelainsäure, Malonsäure, Dodecandisäure, 1,18-Octadecandisäure, Dimersäuren und Alkenyl-Bernsteinsäuren und vorzugsweise Malonsäure.

3. Verfahren nach Anspruch 1, wobei die Quelle eines ersten Koordinationselements Cu²⁺-Ionen in der Lösung vorsieht, vorzugsweise Kupfer(II)-dihydroxidcarbonat.

4. Verfahren nach Anspruch 1, wobei die Quelle eines zweiten Koordinationselements Zn²⁺-Ionen in der Lösung vorsieht, vorzugsweise Zinkcarbonat.

5. Verfahren nach Anspruch 1, wobei die polyfunktionelle Komponente, Kupfer und Zink, der Lösung in einem Molverhältnis von polyfunktioneller Komponente zu Kupfer und Zink von mindestens 3:2 zugegeben wird.

6. Verfahren zum Formulieren eines Produkts, welches das in Anspruch 1 beschriebene Bilden eines Bimetallkomplexes enthält und weiterhin das Kombinieren des so erhaltenen Bimetallkomplexes mit einem pharmazeutisch oder dermatologisch zulässigen Träger umfasst.


8. Verfahren nach Anspruch 6, wobei der Bimetallkomplex dem Produkt in einer Menge von 0,001 bis 5 Gew.-% des Gesamtprodukts zugegeben wird.
9. Zusammensetzung, welche umfasst:
   einen dermatologisch oder pharmazeutisch zulässigen Träger;
   ein oder mehrere Kupfermoleküle;
   ein oder mehrere Zinkmoleküle; und
   eine Zentraleinheit,
   wobei die Zentraleinheit mindestens eine polyfunktionelle Verbindung gewählt aus Dicarbonsäuren, Diaminen
   und Aminosäuren umfasst und die Zentraleinheit das eine oder die mehreren Kupfermoleküle und das eine
   oder die mehreren Zinkmoleküle durch Koordinatenbindung überbrückt.

10. Zusammensetzung nach Anspruch 9, wobei die Zentraleinheit mindestens eine polyfunktionelle Verbindung gewählt
    aus der Gruppe gewählt aus Aminodicarbonsäuren umfasst.

11. Malonatzusammensetzung, welche umfasst:
    ein oder mehrere Kupfermoleküle;
    ein oder mehrere Zinkmoleküle; und
    eine Malonatzentraleinheit,
    wobei die Malonatzentraleinheit das eine oder die mehreren Kupfermoleküle und das eine oder die mehreren
    Zinkmoleküle durch Koordinatenbindung überbrückt.

12. Malonatzusammensetzung nach Anspruch 11, wobei das eine oder die mehreren Kupfermoleküle ein Tetraaqu-
    akupfer(II)-Quadrat ist.

13. Malonatzusammensetzung nach Anspruch 11, wobei das eine oder die mehreren Zinkmoleküle ein Tetraaquazink-
    Quadrat ist.

14. Malonatzusammensetzung nach Anspruch 11, wobei die Zentraleinheit eine achtflächige Diaquadimalonatkuppfer
    (II)-Einheit ist.

15. Zusammensetzung nach Anspruch 9, wobei die Zentraleinheit mehrere Aminosäuren umfasst.

Revendications

1. Procédé de formation d’un complexe bimétallique comprenant
   dissoudre un composant polyfonctionnel choisi dans le groupe constitué par les acides dicarboxyliques, diamines
   et acides aminés dans un solvant pour former une solution ;
   ajouter une source d’un premier élément de coordination à la solution ;
   ajouter une source d’un second élément de coordination à la solution ; et
   récupérer un complexe bimétallique,
   dans lequel les premier et second éléments de coordination sont respectivement du cuivre et du zinc.

2. Procédé selon la revendication 1, dans lequel le composant polyfonctionnel est choisi dans le groupe constitué par
   l’acide maléique, l’acide fumarique, l’acide citraconique, l’acide itaconique, l’acide glutaconique, l’acide phthalique,
   l’acide isophthalique, l’acide tétraphthalique, l’acide cyclohexanedicarboxylique, l’acide succinique, l’acide adipique,
   l’acide sébacique, l’acide azélaïque, l’acide malonique, l’acide dodécansédioïque, l’acide 1,18-octadécanésideioïque,
   les acides dimérisés et les acides alcéni-succiniques, et est de préférence de l’acide malonique.

3. Procédé selon la revendication 1, dans lequel la source d’un premier élément de coordination fournit des ions Cu^{2+}
   dans la solution, de préférence du carbonate cuivrique.

4. Procédé selon la revendication 1, dans lequel la source d’un second élément de coordination fournit des ions Zn^{2+}
   dans la solution, de préférence du carbonate de zinc.

5. Procédé selon la revendication 1, dans lequel le composant polyfonctionnel, du cuivre et du zinc sont ajoutés à la
   solution dans un rapport molaire du composant polyfonctionnel au cuivre et au zinc d’au moins 3:2.
6. Procédé de formulation d’un produit incluant la formation d’un complexe bimétallique comme décrit dans la revendication 1 et comprenant en outre la combinaison du complexe bimétallique ainsi obtenu avec un vecteur pharmaceutiquement ou dermatologiquement acceptable.

7. Procédé selon la revendication 6, comprenant en outre l’ajout dans le produit de l’un ou de plusieurs des éléments choisis dans le groupe comprenant les antimicrobiens, hydratants et agents d’hydratation, agents de pénétration, conservateurs, émulsifiants, huiles naturelles ou synthétiques, solvants, tensio-actifs, détergents, agents gélifiants, émollients, antioxydants, fragrances, charges, épaisseurs, cires, absorbants d’odeur, colorants, agents colorants, poudres, agents de contrôle de la viscosité et l’eau, et en option l’ajout d’anesthésiques, actifs anti-démangeaisons, extraits de plantes, agents de conditionnement, agents opacifiants ou éclaircissants, paillettes, humectants, mica, minéraux, polyphénols, silicones ou dérivés de celles-ci, écrans solaires, vitamines et agents phytothérapeutiques.

8. Procédé selon la revendication 6, dans lequel le complexe bimétallique est ajouté au produit dans une quantité allant de 0,001 à 5 % en poids du produit global.

9. Composition comprenant :
   - un vecteur dermatologiquement ou pharmaceutiquement acceptable ;
   - une ou plusieurs molécules de cuivre ;
   - une ou plusieurs molécules de zinc ; et
   - un motif central,
   dans lequel le motif central comprend au moins un composé polyfonctionnel choisi parmi les acides dicarboxyliques, diamines, et acides aminés et le motif central relie l’une ou les plusieurs molécules de cuivre et l’une ou les plusieurs molécules de zinc par liaison de coordination.

10. Composition selon la revendication 9, dans laquelle le motif central comprend au moins un composé polyfonctionnel choisi dans le groupe choisi parmi les acides aminés dicarboxyliques.

11. Composition de malonate comprenant :
   - une ou plusieurs molécules de cuivre ;
   - une ou plusieurs molécules de zinc ; et
   - un motif central de malonate,
   dans lequel le motif central de malonate relie l’une ou les plusieurs molécules de cuivre et l’une ou les plusieurs molécules de zinc par liaison de coordination.

12. Composition de malonate selon la revendication 11, dans laquelle l’une ou les plusieurs molécules de cuivre sont un carré de cuivre (II) tétrahydraté.

13. Composition de malonate selon la revendication 11, dans laquelle l’une ou les plusieurs molécules de zinc sont un carré de zinc tétrahydraté.

14. Composition de malonate selon la revendication 11, dans laquelle le motif central est une entité dimalonate de cuivre(II) dihydraté octaèdre.

15. Composition selon la revendication 9, dans laquelle le motif central comprend une pluralité d’acides aminés.
REFERENCES CITED IN THE DESCRIPTION

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Patent documents cited in the description

- US 11452642 B [0048]

Non-patent literature cited in the description