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(73) Patenthaver: **Kindeva Drug Delivery L.P., 42 Water Street, Building 75, St. Paul, MN 55170, USA**

(72) Opfinder: **BROWN, Kenneth E., 3M Center, Post Office Box 33427, Saint Paul, Minnesota 55133-3427, USA**
DOHMEIER, Daniel M., 3M Center, Post Office Box 33427, Saint Paul, Minnesota 55133-3427, USA
MOSEMAN, Joan T., 3M Center, Post Office Box 33427, Saint Paul, Minnesota 55133-3427, USA
ZHANG, Ying, 3M Center, Post Office Box 33427, Saint Paul, Minnesota 55133-3427, USA
HATTERSLEY, Gary, 950 Winter Street, Waltham, Massachusetts 02451, USA
HARRIS, Alan, 205 East 85th Street Apt. 4C, New York City, NY 10028, USA
DICK, Lisa A., Afton, Minnesota, P.O.Box 33427, Saint Paul, Minnesota 55133-3427, USA

(74) Fuldmægtig i Danmark: **Plougmann Vingtoft A/S, Strandvejen 70, 2900 Hellerup, Danmark**

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DESCRIPTION

FIELD

[0001] The present disclosure relates to a medical device comprising a microneedle array and a useful composition.

BACKGROUND

[0002] Only a limited number of molecules with demonstrated therapeutic value can be transported through the skin, even with the use of approved chemical enhancers. The main barrier to transport of molecules through the skin is the stratum corneum (the outermost layer of the skin).

[0003] Devices including arrays of relatively small structures, sometimes referred to as microneedles or micro-pins, have been disclosed for use in connection with the delivery of therapeutic agents and other substances through the skin and other surfaces. The devices are typically pressed against the skin in an effort to pierce the stratum corneum such that the therapeutic agents and other substances can pass through that layer and into the tissues below

[0004] Microneedle devices having a fluid reservoir and conduits through which a therapeutic substance may be delivered to the skin have been proposed, but there remain a number of difficulties with such systems, such as the ability to make very fine channels that can reliably be used for fluid flow.

[0005] Microneedle devices having a dried coating on the surface of a microneedle array have desirable features compared to fluid reservoir devices. The devices are generally simpler and can directly introduce a therapeutic substance into the skin without the need for providing reliable control of fluid flow through very fine channels in the microneedle device.

[0006] Coated microneedle devices typically deliver therapeutic substances into the intradermal space and it is known that at least in some instances the pharmacokinetic profile obtained with intradermal delivery may differ from that of other delivery routes, such as subcutaneous and intravenous. US 2009/0016935 A1 describes formulations for coating asperities, such as microneedles, which comprises a biologically active agent and a polyphosphazene polyelectrolyte.

BRIEF SUMMARY

[0007] In one embodiment, the disclosure is a medical device comprising a composition comprising a therapeutically active amount of an active agent, a zinc compound selected from the group consisting of zinc, pharmaceutically acceptable salts of zinc, and mixtures thereof, and an array of microneedles, wherein at least a portion of the composition is present as a coating on at least a portion of the microneedles, wherein the active agent is a protein or peptide, and wherein the zinc compound comprises an inorganic salt of zinc.

[0008] In one embodiment, the disclosure is a composition as defined above for use as a medicament in a device as defined above, wherein said composition is to be delivered to a mammal by applying said device to a skin surface of a mammal,
allowing the device to remain in contact with the skin for a period of time to allow a portion of the active agent to be transferred into the skin of the mammal, and subsequently removing the device from the mammal.

BRIEF DESCRIPTION OF THE DRAWINGS

[0009] The disclosure may be more completely understood in consideration of the following detailed description of various embodiments of the disclosure in connection with the accompanying drawings, in which:

FIG. 1 is a schematic cross-sectional view of an uncoated microneedle array.

FIG. 2 is a schematic perspective view of a patch microneedle device.

[0010] The figures are not necessarily to scale. Like numbers used in the figures refer to like components. However, it will be understood that the use of a number to refer to a component in a given figure is not intended to limit the component in another figure labeled with the same number.

FIG. 3 is a graph of plasma PTH concentration/Cmax vs. time.

FIG. 4 is a graph of plasma rhGH concentration/Cmax vs. time.

DETAILED DESCRIPTION

[0011] In the following description, reference is made to the accompanying drawing that forms a part hereof, and in which are shown by way of illustration several specific embodiments.

[0012] The following detailed description, therefore, is not to be taken in a limiting sense.

[0013] All scientific and technical terms used herein have meanings commonly used in the art unless otherwise specified. The definitions provided herein are to facilitate understanding of certain terms used frequently herein and are not meant to limit the scope of the present disclosure.

[0014] As used in this specification and the appended claims, the singular forms "a", "an", and "the" encompass embodiments having plural referents, unless the content clearly dictates otherwise. As used in this specification and the appended claims, the term "or" is generally employed in its sense including "and/or" unless the content clearly dictates otherwise.

[0015] Compositions disclosed herein include at least one active pharmaceutical ingredient (referred to herein as an "API" or active agent); and an excipient comprising a zinc compound. According to the claims the zinc compound is selected from the group consisting of zinc, pharmaceutically acceptable salts of zinc, and mixtures thereof, and comprises an inorganic salt of zinc.

[0016] Suitable inorganic salts of zinc may include, for example, zinc chloride. In one embodiment the zinc compound comprises zinc chloride.

[0017] In one embodiment the zinc compound consists essentially of zinc chloride. By consists essentially of zinc chloride, it is meant that the zinc compound of the disclosure may contain minimal amounts of zinc or other salts of zinc to the extent that these minimal amounts have no detectable effect on the functional properties of the composition, such as the effect on pharmacokinetic parameters such as Cmax and AUC, as described in more detail below. It should be understood that if only minimal amounts of compounds other than zinc chloride are present, such as if 99% or more by weight of the total zinc compound is zinc chloride, then the zinc compound consists essentially of zinc chloride. In one embodiment, the zinc compound consists of zinc chloride.

[0018] In one embodiment 90% or more by weight of the zinc compound is present as zinc chloride. In one embodiment 95% or more by weight of the zinc compound is present as zinc chloride. In one embodiment 98 % or more by weight of the zinc compound is present as zinc chloride. In one embodiment 99% or more by weight of the zinc compound is present as zinc chloride.

[0019] Also described herein but not claimed are medical devices wherein
the zinc compound consists essentially of zinc acetate. By consists essentially of zinc acetate, it is meant that the zinc compound of the disclosure may contain minimal amounts of zinc or other salts of zinc to the extent that these minimal amounts have no detectable effect on the functional properties of the composition, such as the effect on pharmacokinetic parameters such as Cmax and AUC, as described in more detail below. It should be understood that if only minimal amounts of compounds other than zinc acetate are present, such as if 99% or more by weight of the total zinc compound is zinc acetate, then the zinc compound consists essentially of zinc acetate; the zinc compound may consist of zinc acetate.

[0020] In embodiments, the molar ratio of zinc compound to API is greater than 0.1, greater than 0.2, or greater than 0.25. In embodiments, the molar ratio of zinc compound to API is less than 2.0, less than 1.5, or less than 1.0. In one embodiment, the molar ratio of zinc compound to API is between 0.1 and 2.0. In one embodiment, the molar ratio of zinc compound to API is between 0.2 and 1.5. In one embodiment, the molar ratio of zinc compound to API is between 0.25 and 1.0. In one embodiment, the molar ratio of zinc compound to API is about 0.5. In one embodiment, the molar ratio of zinc compound to API is about 0.75. In one embodiment, the molar ratio of zinc compound to API is about 1.0.

[0021] In embodiments, the amount of zinc compound is greater than 0.5%, greater than 1%, or greater than 2% of the total weight of the composition. In embodiments, the amount of zinc compound is less than 10%, less than 8%, or less than 6% of the total weight of the composition. In one embodiment, the amount of zinc compound is between 0.5 and 10% of the total weight of the composition. In one embodiment, the amount of zinc compound is between 1 and 8% of the total weight of the composition. In one embodiment, the amount of zinc compound is between 2 and 6% of the total weight of the composition. In one embodiment, the amount of zinc compound is about 3% of the total weight of the composition. In one embodiment, the amount of zinc compound is about 4% of the total weight of the composition. In one embodiment, the amount of zinc compound is about 5% of the total weight of the composition.

[0022] The at least one API can generally include any pharmacologically active component like vaccines, hormones, proteins, peptides, lipoproteins, glycoproteins, polysaccharides, lipopolysaccharides, oligosaccharides, glycolipids, polynucleotide sequences, DNA vaccines, and antibiotics such as ceftriaxone.

[0023] According to the claims the composition comprises an API that is a protein or a peptide.

[0024] According to an aspect described herein the at least one API can also include a small molecule that may be otherwise difficult or impossible to deliver by passive transdermal delivery. Examples of such molecules include ionic molecules, such as bisphosphonates, for example sodium alendronate or pamedronate; molecules with physicochemical properties that are not conducive to passive transdermal delivery such as naltrexone, and lidocaine for example.

[0025] The at least one API can also include agents for dermatological treatments, vaccine delivery, or enhancement of an immune response with vaccine adjuvants. Examples of suitable vaccines include DNA vaccine, cellular vaccines such as a dendritic cell vaccine, recombinant protein vaccine, therapeutic cancer vaccine, anthrax vaccine, flu vaccine, Lyme disease vaccine, rabies vaccine, measles vaccine, mumps vaccine, chicken pox vaccine, small pox vaccine, hepatitis vaccine, hepatitis A vaccine, hepatitis B vaccine, hepatitis C vaccine, pertussis vaccine, rubella vaccine, diphtheria vaccine, encephalitis vaccine, Japanese encephalitis vaccine, respiratory syncytial virus vaccine, yellow fever vaccine, polio vaccine,

herpes vaccine, human papilloma virus vaccine, rotavirus vaccine, pneumococcal vaccine, meningitis vaccine, whooping cough vaccine, tetanus vaccine, typhoid fever vaccine, cholera vaccine, tuberculosis vaccine, severe acute respiratory syndrome (SARS) vaccine, HSV-1 vaccine, HSV-2 vaccine, HIV vaccine and combinations thereof. The term "vaccine" thus includes antigens in the forms of proteins, peptides, lipoproteins, glycoproteins, polysaccarides, lipopolysaccharides, oligosaccarides, glycolipids, polynucleotide sequences, weakened or killed viruses, virus particles, virus-like particles, weakened or killed bacteria, bacterial cell walls, toxoids, and desensitizing agents such as cat, dust, or pollen allergens. Additional examples of suitable vaccines and vaccine adjuvants are described in United States Patent Application Publication Nos. 2004/0049150, 2004/0265354, and US2006/0195067.

[0026] In embodiments that include an API that is a vaccine, the aqueous formulation can also optionally include one or more adjuvants. An adjuvant is an agent that modifies the effect of another agent (in this case the vaccine API). Adjuvants are often utilized to enhance the recipient's immune response to the vaccine. The particular identity of the adjuvant can depend at least in part on the identity of the API vaccine. Adjuvants can include aluminum phosphate, aluminum phosphate gel, aluminum hydroxide, squalene, beta-glucan, CpG containing oligonucleotides, QS-21, glucosaminylmuramyl dipeptide (GMDP), murametide, dimethyldioctadecylammonium bromide (DDA), Quil A, threonyl-muramyl dipeptide (threonyl-MDP), MTP-PE, MTP-PE liposomes, a 4-amino-imidazo[4,5-c]quinoline based immune response modifier compound, a 4-amino[1,3]thiazolo[4,5-c]quinoline based immune response modifier compound, a TLR6 agonist, a TLR7 agonist, a TLR8 agonist, a TLR9 agonist, imiquimod, resiquimod, 2-propyl[1,3]thiazolo[4,5-c]quinolin-4-amine, IL-2, IL-4, IL-10, IL-12, IL-15, IL-18, and combinations thereof.

[0027] In embodiments, the at least one API can be a composition of matter or mixture containing a component that is pharmacologically effective when administered in an amount of less than about 5 mg, and in some embodiments less than about 0.25 mg.

[0028] In embodiments the API includes, for example, human growth hormone (hGH), tissue plasminogen activator (TPA), calcitonin gene related peptide (CGRP), leutinizing hormone releasing hormone (LHRH), LHRH analogs (such as goserelin, leuprolide, buserelin, triptorelin), gonadorelin, and napfarelin, menotropins (follicle stimulating hormone (FSH) and leutinizing hormone (LH)), human menopausal goanadotropins (hMG), human chorionic gonadotropin (hCG), vasopressin, desmopressin, insulin, adrenocortiocotropic hormone (ACTH), ACTH analogs such as ACTH (1-24), calcitonin, parathyroid hormone (PTH), parathyroid hormone antagonists, parathyroid horomone-related protein (PTHrP), parathyroid hormone-related protein analogues, which can be, without limitation, one or more of, oxytocin, deamino [Val4, D-Arg8] arginine vasopressin, interferon alpha, interferon beta, interferon gamma, tumor necrosis factor (TNF), erythropoietin (EPO), granulocyte macrophage colony stimulating factor (GM-CSF), granulocyte colony stimulating factor (G-CSF), interleukins, IL-2 (IL-2), interleukin-10 (IL-10), glucagon, and growth hormone releasing factor (GRF). The agents can be in various forms, such as free bases, acids, charged or uncharged molecules, components of molecular complexes or nonirritating, pharmacologically acceptable salts. Also,

simple derivatives of the agents (such as ethers, esters, amides, etc) which are physiologically hydrolyzed at body pH, enzymes, etc., can be employed.

[0029] In embodiments the API includes, for example, human growth hormone (hGH), tissue plasminogen activator (TPA), calcitonin gene related peptide (CGRP), leutinizing hormone releasing hormone (LHRH), LHRH analogs (such as goserelin, leuprolide, buserelin, triptorelin), gonadorelin, and napfarelin, menotropins (follicle stimulating hormone (FSH) and leutinizing hormone (LH)), human menopausal goanadotropins (hMG), human chorionic gonadotropin (hCG), vasopressin, desmopressin, insulin, adrenocortiocotropic hormone (ACTH), ACTH analogs such as ACTH (1-24), calcitonin, parathyroid hormone (PTH), parathyroid hormone antagonists, parathyroid horomone-related protein (PTHrP), oxytocin, deamino [Val4, D-Arg8] arginine vasopressin, interferon alpha, interferon beta, interferon gamma, tumor necrosis factor (TNF), erythropoietin (EPO), granulocyte macrophage colony stimulating factor (GM-CSF), granulocyte colony stimulating factor (G-CSF), interleukins, IL-2 (IL-2), interleukin-10 (IL-10), glucagon, and growth hormone releasing factor (GRF). The agents can be in various forms, such as free bases, acids, charged or uncharged molecules, components of molecular complexes or nonirritating, pharmacologically acceptable salts. Also, simple derivatives of the agents (such as ethers, esters, amides, etc) which are physiologically hydrolyzed at body pH, enzymes, etc., can be employed.

[0030] In some embodiments, the active is not a parathyroid hormone-related protein analogue.

[0031] Compositions can also include additional components, such as a second (or subsequent) API, a second (or subsequent) excipient, components not noted herein, or some combination thereof.

[0032] Additional excipients can function, for example, to maintain the active nature of the API, to facilitate the coating performance of the formulation, or a combination thereof. The particular excipient to be utilized can depend at least in part on the particular API (or APIs) that are included in the composition.

[0033] Exemplary excipients can include for example buffers, carbohydrates, polymers, amino acids, polyamino acids, surfactants, proteins, non-aqueous solvents, inorganic salts, acids, bases, antioxidants and saccharin.

[0034] In embodiments, disclosed compositions can optionally include at least one buffer as an excipient. A buffer can generally function to stabilize the pH of an aqueous formulation that can be used to prepare the disclosed compositions. The particular buffer to be utilized can depend at least in part on the particular API (or APIs) that are included in the aqueous formulation. The pH of the aqueous formulation can be important, for example, to maintain the solubility of the API at a desired level. Generally, any commonly utilized buffers can be used in disclosed aqueous formulations and compositions.

[0035] Exemplary buffers can include for example, histidine, phosphate buffers, acetate buffers, citrate buffers, glycine buffers, ammonium acetate buffers, succinate buffers, pyrophosphate buffers, Tris acetate (TA) buffers, and Tris buffers. Buffered saline solutions can also be utilized as buffers. Exemplary buffered saline solutions include, for example, phosphate buffered saline (PBS), Tris buffered saline (TBS), saline-sodium acetate buffer (SSA), saline-sodium citrate buffer (SSC). In embodiments, PBS can be utilized as the buffer.

[0036] In embodiments, compositions can optionally include at least one carbohydrate, such as a sugar. Suitable sugars can include for example non-reducing sugars such as raffinose, stachyose, sucrose, and trehalose; and reducing sugars such as monosaccharides and disaccharides. Exemplary monosacharides can include apiose, arabinose, digitoxose, fucose, fructose, galactose, glucose, gulose, hamamelose, idose, lyxose, mannose, ribose, tagatose, and xylose. Exemplary disaccharides can include for example cellobiose, gentiobiose, lactose, lactulose, maltose, melibiose, primeverose, rutinose, scillabiose, sophorose, turanose, and vicianose. In embodiments, sucrose, trehalose, fructose, maltose, or combinations thereof can be utilized. All optical isomers of exemplified sugars (D, L, and racemic mixtures) are also included herein.

[0037] In embodiments, compositions can optionally include at least one carbohydrate, such as a polysaccharide. Suitable polysaccharides can include for example starches such as hydroxyethyl starch, pregelantized corn starch, pentastarch, dextrin, dextran or dextran sulfate, gamma-cyclodextrin, alpha-clyclodextrin, beta-clyclodextrin, glucosyl-alpha-cyclodextrin, maltosyl-alpha-cyclodextrin, glucosyl-beta-cyclodextrin, maltosyl-beta-cyclodextrin, 2-hydroxy-beta-cyclodextrin, 2-hydroxypropyl-beta-cyclodextrin, 2-hydroxypropyl-gamma-cyclodextrin, hydroxyethyl-beta-cyclodextrin, methyl-beta-cyclodextrin, sulfobutylether-alpha-cyclodextrin, sulfobutylether-beta-cyclodextrin, and sulfobutylether-gamma-cyclodextrin. In embodiments, hydroxyethyl starch, dextrin, dextran, gamma-cyclodextrin, beta-cyclodextrin, or combinations thereof can be utilized. In embodiments, dextrans having an average molecular mass of 35,000 to 76,000 can be utilized.

[0038] In embodiments, compositions can optionally include at least one carbohydrate, such as a cellulose. Suitable celluloses can include for example hydroxyethyl cellulose (HEC), methyl cellulose (MC), microcrystalline cellulose, hydroxypropyl methyl cellulose (HPMC), hydroxyethylmethyl cellulose (HEMC), hydroxypropyl cellulose (HPC), and mixtures thereof.

[0039] In embodiments, compositions can optionally include at least one polymer, such as for example, polyvinyl pyrrolidone (PVP), polyethylene glycol (PEG), polyvinyl alcohol (PVA), and polyethylene glycol sorbitan isostearate. In embodiments, polyvinyl pyrrolidones (PVP) having an average molecular weight of 10,000 can be utilized. In embodiments, polyvinyl pyrrolidones (PVP having an average molecular weight of 5,000 to 1.5 million can be utilized. In embodiments, polyethylene glycols having an average molecular weight of 300 to 8,000 can be utilized.

[0040] In embodiments, compositions can optionally include at least one amino acid. Suitable

amino acids can include for example lysine, histidine, cysteine, glutamate, lysine acetate, sarcosine, proline, threonine, asparagine, aspartic acid, glutamic acid, glutamine, isoleucine, leucine, methionine, phenylalanine, serubem tryptophan, tyrosine, valine, alanine, agrinine, and glycine. In many cases the salt form of the amino acids can be used to increase the aqueous solubility of the amino acid in the compositions. In a preferred embodiment the compositions include histidine.

[0041] In embodiments, compositions can optionally include at least one polyamino acid. Suitable polyamino acids can include for example polyhistidine, polyaspartic acid, and polylysine. In embodiments, compositions can include at least one protein. Suitable proteins can include for example human serum albumin and bioengineered human albumin.

[0042] In embodiments, compositions can optionally include at least one surfactant which can be amphoteric, cationic, anionic, or nonanionic. Suitable surfactants can include for example lecithin, polysorbates (such as polysorbate 20, polysorbate 40, and polysorbate 80 for example), glycerol, sodium lauroamphoacetate, sodium dodecyl sulfate, cetylpyridinium chloride (CPC), dodecyltrimethyl ammonium chloride (DoTAC), sodium desoxycholate, benzalkonium chloride, sorbitan laurate, and alkoxylated alcohols (such as laureth-4).

[0043] In embodiments, compositions can optionally include at least one non-zinc containing inorganic salt. Suitable inorganic salts can include for example sodium chloride, and potassium chloride.

[0044] In embodiments, compositions can optionally include saccharin, for example saccharin sodium dihydrate. In embodiments, compositions can optionally include a lipid such as dipalmitoylphosphatidylcholine (DPPC) for example.

[0045] In embodiments, compositions can optionally include at least one weak acid, weak base, strong acid, strong base, or some combination thereof. Acids and bases can serve the purpose of solubilizing or stabilizing the API. These acids and bases can be referred to as counterions. These acids and bases can be organic or inorganic. Exemplary weak acids include for example acetic acid, propionic acid, pentanoic acid, citric acid, succinic acid, glycolic acid, gluconic acid, glucuronic acid, lactic acid, malic acid, pyruvic acid, tartaric acid, tartronic acid, fumaric acid, glutamic acid, aspartic acid, malonic acid, butyric acid, crotonic acid, digylcolide acid, and glutaric acid. Exemplary strong acids include for example hydrochloric acid, hydrobromic acid, nitric acid, sulfonic acid, sulfuric acid, maleic acid, phosphoric acid, benzene sulfonic acid, and methane sulfonic acid. Exemplary weak bases include for example ammonia, morpholine, histidine, lysine, arginine, monoethanolamine, diethanolamine, triethanolamine, tromethamine, methylglucamine, and glucosamine. Exemplary strong bases include for example sodium hydroxide, potassium hydroxide, calcium hydroxide, and magnesium hydroxide.

[0046] In embodiments, compositions can optionally include at least one antioxidant. Suitable antioxidants can include for example sodium citrate, citric acid, EDTA, ascorbic acid,

methionine, sodium ascorbate, and combinations thereof.

[0047] The amounts of the various components in disclosed compositions can vary depending on the identity of the components in the components, the amount of API desired on the microneedle array, the amount of zinc compound present in the composition, the type of microneedle array being coated, other considerations not discussed herein, or some combination thereof.

[0048] Compositions can also be characterized based on the amount of API in the composition. In embodiments, a disclosed composition can have from 0.01% to 80% by weight of the at least one API; or from 0.1% to 70% by weight of the at least one API. In embodiments where an optional carbohydrate is employed, the compositions can also be characterized based on the amount of carbohydrate in the composition. In embodiments, a disclosed composition can have from 0% to 80% by weight of at least one carbohydrate; or from 5% to 70% by weight of at least one carbohydrate. In compositions where an optional polymer is employed, compositions can also be characterized based on the amount of polymer in the composition. In embodiments, a disclosed composition can have from 0% to 50% by weight of at least one polymer; or from 1% to 20% by weight of at least one polymer. In compositions where an optional surfactant is employed, compositions can also be characterized based on the amount of surfactant in the composition. In embodiments, a disclosed composition can have from 0% to 10% by weight of at least one surfactant; or from 0% to 5% by weight of at least one surfactant.

[0049] Compositions disclosed herein are typically prepared by coating a liquid formulation onto a microneedle array and then drying the liquid formulation so as to leave a dried composition on the microneedle array. The liquid formulations can also be referred to as coating formulations. Coating formulations disclosed herein can be further described by various properties of the formulations. Exemplary properties that can be utilized to further describe the coating formulations include for example, the viscosity of the coating formulation, the surface tension of the coating formulation, the contact angle of the coating formulation on the material of the microneedle material, or some combination thereof.

[0050] Coating formulations disclosed herein often include water as a solvent and may also be referred to as aqueous formulations. Generally, the solvent composition in a coating formulation is selected such that it may dissolve or disperse the active pharmaceutical ingredient and excipients. Aqueous formulations disclosed herein can also include co-solvents in addition to water. In embodiments, an aqueous formulation can optionally include additional solvents (also referred to as co-solvents) such as ethanol, iospropanol, methanol, propanol, butanol, propylene glycol, dimethysulfoxide, glycerin, 1-methyl-2-pryrrolidinone, or N,N-dimethylformamide.

[0051] In embodiments, a coating formulation can be further characterized by its viscosity. Generally, viscosity is a measurement of the resistance of a fluid which is being deformed by either shear stress or tensile stress. In embodiments, disclosed coating formulations can be

characterized by their resistance to being deformed by a shear stress, which can also be referred to as the shear viscosity of the aqueous formulation. Various instruments can be used for viscosity testing, including rheometers. In embodiments, the viscosity of a coating formulation can be measured using a rheometer, for example rheometers from TA Instruments (New Castle, DE).

[0052] In embodiments, coating formulations disclosed herein can have a viscosity (or shear viscosity) of from 500 to 30,000 mPa·s (500 to 30,000 centipoise (cps)) when measured at a shear rate of $100s^{-1}$ at a temperature of 25° C. In embodiments, coating formulations disclosed herein can have a viscosity (or shear viscosity) of from '500 to 10,000 mPa·s (500 to 10,000 cps) when measured at a shear rate of $100s^{-1}$ at a temperature of 25° C. In embodiments, coating formulations disclosed herein can have a viscosity (or shear viscosity) of from 500 to 8,000 mPa·s (500 to 8,000 cps) when measured at shear rate of $100s^{-1}$ at a temperature of 25°C.

[0053] In embodiments, a coating formulation can be further characterized by its surface tension. Various methods can be utilized to measure surface tension. An exemplary type of surface tension measurement is based on the pendant drop method. In a pendant drop method of measuring surface tension, a drop of liquid is suspended from the end of a tube by surface tension. The force due to surface tension is proportional to the length of the boundary between the liquid and the tube. Various instruments that encompass optics systems for measuring the relevant parameters of the drop and software packages for calculating the surface tension based on the measured parameters can be utilized herein. An exemplary instrument includes the Drop Shape Analysis System (Model DSA 100S) available from Krüss (Hamburg, Germany).

[0054] In embodiments, coating formulations disclosed herein can have a surface tension (measured at ambient, or room temperature conditions) that is not greater than 60 mN/m (60 dynes/cm). In embodiments, coating formulations disclosed herein can have a surface tension that is not greater than 55 mN/m (55 dynes/cm). In embodiments, coating formulations disclosed herein can have a surface tension from 40 to 55 mN/m (40 dynes/cm to 55 dynes/cm).

[0055] In embodiments, a coating formulation can be further characterized by its contact angle with the material of the microneedles (also referred to as the "microneedle material"). It should be noted that the contact angle of the coating formulation with respect to the microneedle material is measured on a horizontal substrate made of the microneedle material. The microneedle material can be (or include) silicon or a metal such as stainless steel, titanium, or nickel titanium alloy. The microneedle material can also be (or include) a medical grade polymeric material. Generally, the contact angle of a disclosed coating formulation with the microneedle material is an indication of the affinity of the coating formulation for the microneedle material. The lower the contact angle is, the stronger the attraction of the coating formulation for the microneedle material, resulting in increased wetting of the microneedle

surface. The contact angle of the aqueous formulation on the microneedle material can be measured using various methods. In embodiments, the contact angle of the aqueous formulation on the microneedle material can be measured using the sessile drop method for example. Generally, a goniometer (or an instrument that employs a goniometer) can be utilized to measure contact angles, an example of such an instrument is the Drop Shape Analysis System (Model DSA 100S) available from Krüss (Hamburg, Germany). In embodiments, the contact angle can be measured within 5 seconds of the transfer of the coating formulation onto the substrate.

[0056] In embodiments, coating formulations disclosed herein can have a contact angle (measured at ambient, or room temperature conditions) with the microneedle material of 50° or greater. In embodiments, coating formulations disclosed herein can have a contact angle of 55° or greater. In embodiments, coating formulations disclosed herein can have a contact angle of 65° or greater. In embodiments, coating formulations disclosed herein can have a contact angle of 90° or less. In embodiments, coating formulations disclosed herein can have a contact angle of 80° or less.

[0057] In embodiments, the microneedle material can be a medical grade polymeric material. Exemplary types of medical grade polymeric materials include for example, polycarbonate and liquid crystalline polymer (referred to herein as "LCP").

[0058] Also disclosed herein is a composition as defined herein for use as a medicament in a device, wherein said composition is to be delivered to a mammal by applying said device to the skin of a mammal wherein the device comprises an array of microneedles and the compositions disclosed herein and the composition is present as a coating on at least a portion of the microneedles; the device is allowed to remain in contact with the skin for a period of time to allow a portion of the active agent to be transferred into the skin of the mammal and is subsequently removed from the mammal.

[0059] Some examples of suitable mammals include humans, primates, pigs, cats, dogs, and rodents. In some embodiments the mammal is a human.

[0060] In some embodiments, the peak serum concentration of the active agent or C_{max} attained in the mammal is greater than the C_{max} that would be obtained if a like device with a composition lacking the zinc compound were applied to a mammal for a period of time. That is, inclusion of the zinc compound in the formulation causes an increase in C_{max}. In some embodiments, C_{max} is about 1.2 times more than, about 1.5 times more than, or about 2 times more than a comparable device with a like composition lacking the zinc compound.

[0061] In some embodiments, the area-under-the-curve or AUC attained in the mammal is greater than the AUC that would be obtained if a like device with a composition lacking the zinc compound were applied to a mammal for a period of time. That is, inclusion of the zinc compound in the formulation causes an increase in AUC. In some embodiments, AUC is about

1.2 times more than, about 1.5 times more than, or about 2 times more than a comparable device with a like composition lacking the zinc compound.

[0062] In some embodiments, the bioavailability of the active agent attained in the mammal is greater than the bioavailability that would be obtained if a like device with a composition lacking the zinc compound were applied to a mammal for a period of time. That is, inclusion of the zinc compound in the formulation causes an increase in bioavailability. In some embodiments, the bioavailability is about 1.2 times more than, about 1.5 times more than, or about 2 times more than a comparable device with a like composition lacking the zinc compound.

[0063] In some embodiments, the time to achieve peak serum concentration of the active agent or T_{max} attained in the mammal is greater than the T_{max} that would be obtained if a like device with a composition lacking the zinc compound were applied to a mammal for a period of time. That is, inclusion of the zinc compound in the formulation causes an increase in T_{max}. In some embodiments, T_{max} is about 1.2 times more than, about 1.5 times more than, or about 2 times more than a comparable device with a like composition lacking the zinc compound.

[0064] The period of time that the device is allowed to remain in contact with the skin may be chosen according to the active agent and type of composition used to achieve a desired therapeutic result. In some embodiments, the device is allowed to remain in contact with the skin for more than about 1 second, more than about 10 seconds, more than about 30 seconds, more than about 1 minute, or more than about 5 minutes. In some embodiments, the device is allowed to remain in contact with the skin for less than about 60 minutes, less than about 30 minutes, less than about 10 minutes, less than about 5 minutes, less than about 2 minutes, or less than about 1 minute. In some embodiments, the device is allowed to remain in contact with the skin for between about 10 seconds and 10 minutes, between about 30 seconds and 5 minutes, or between about 30 seconds and about 2 minutes.

[0065] Generally, an "array" refers to medical devices described herein that include more than one (in embodiments, a plurality) structure capable of piercing the stratum corneum to facilitate the transdermal delivery of therapeutic agents or the sampling of fluids through or to the skin. The terms "microstructure", or "microneedle" refer to the structures associated with an array that are capable of piercing the stratum corneum to facilitate the transdermal delivery of therapeutic agents or the sampling of fluids through or to the skin. By way of example, microstructures can include needle or needle-like structures as well as other structures capable of piercing the stratum corneum. The term "microneedle array" therefore can refer to a plurality of structures that are capable of piercing the stratum corneum to facilitate the transdermal delivery of therapeutic agents or the sampling of fluids through or to the skin.

[0066] Microneedle arrays useful in disclosed embodiments may include any of a variety of configurations, such as those described in the following patents and patent applications.

[0067] One embodiment for the microneedle arrays includes the structures disclosed in U. S. Patent Application Publication No. 2005/0261631,

which describes microneedles having a truncated tapered shape and a controlled aspect ratio. A further embodiment for the microneedle arrays includes the structures disclosed in U.S. Patent No. 6,881,203,
which describes tapered microneedles with at least one channel formed on the outside surface. Another embodiment for the microneedle arrays includes the structures disclosed in U.S. Provisional Patent Application 61/168,268 and U.S. Provisional Patent Application 61/115,840,
which both describe hollow microneedles.

[0068] Generally, a microneedle array can include a plurality of microneedles. **FIG. 1** shows a portion of a microneedle array **200** that includes four microneedles **210** (of which two are referenced in **FIG. 1)** positioned on a microneedle substrate **220**. Each microneedle **210** has a height **h**, which is the length from the tip of the microneedle **210** to the microneedle substrate **220**. Either the height of a single microneedle or the average height of all microneedles on the microneedle array can be referred to as the height of the microneedle, **h**. In embodiments, each of the plurality of microneedles (or the average of all of the plurality of microneedles) can have a height of about 1 to 1200 micrometers (μm). In embodiments, each of the plurality of microneedles can have a height of about 1 to 1000 μm. In embodiments, each of the plurality of microneedles can have a height of about 200 to 750 μm.

[0069] A single microneedle or the plurality of microneedles in a microneedle array can also be characterized by their aspect ratio. The aspect ratio of a microneedle is the ratio of the height of the microneedle, **h**, to the width (at the base of the microneedle), **w** (as seen in **FIG. 1)**. The aspect ratio can be presented as **h**:**w**. In embodiments, each of the plurality of microneedles (or the average of all of the plurality of microneedles) can have an aspect ratio in the range of 2:1 to 5:1. In embodiments, each of the plurality of microneedles can have an aspect ratio of at least 2:1. In embodiments, each of the plurality of microneedles can have an aspect ratio of at least 3:1.

[0070] In embodiments, a microneedle or the plurality of microneedles in a microneedle array can also be characterized by their shape. In embodiments, each of the plurality of microneedles can have a square pyramidal shape or the shape of a hypodermic needle.

[0071] In embodiments a single microneedle or the plurality of microneedles in a microneedle array can also be characterized by its internal structure. In embodiments, each of the plurality of microneedles can have a cavity (for example a cylindrical cavity) extending the entire length of the microneedle (hollow microneedle), a cavity (for example a cylindrical cavity) extending through a portion of the microneedle (a partially hollow microneedle), or no internal cavity in the microneedle (solid microneedle). An internal cavity can provide a microneedle with additional surface area for coating the formulation and may allow for higher concentrations of API to be coated onto a microneedle.

[0072] In embodiments, a microneedle array may be applied to a skin surface in the form of a patch. Such an embodiment is shown in more detail in **FIG. 2**. **FIG. 2** illustrates a device

comprising a patch **20** in the form of a combination of a microneedle array **22**, pressure sensitive adhesive **24** and backing **26**. Such a patch **20**, or a device including multiple microneedle arrays or multiple patches **20** can be referred to as a delivery device. A portion of the microneedle array **22** is illustrated with microneedles **10** protruding from a microneedle substrate **14**. The microneedles **10** may be arranged in any desired pattern or distributed over the microneedle substrate **14** randomly. As shown, the microneedles **10** are arranged in uniformly spaced rows. In one embodiment, microneedle arrays can have a distal-facing surface area of more than about 0.1 cm^2 and less than about 20 cm^2; in embodiments more than about 0.5 cm^2 and less than about 5 cm^2. In one embodiment (not shown), a portion of the substrate **14** of the patch **20** is non-patterned. In one embodiment the non-patterned surface has an area of more than about 1 percent and less than about 75 percent of the total area of the device surface that faces a skin surface of a patient. In one embodiment the non-patterned surface has an area of more than about 0.10 square inch (0.65 cm^2) to less than about 1 square inch (6.5 cm^2). In another embodiment (shown in **FIG. 2**), the microneedles are disposed over substantially the entire surface area of the array **22**.

[0073] Once at least a portion of the solvent from the aqueous formulation has evaporated (either from a single contact step or multiple contact steps), the aqueous formulation on the microneedle array can be referred to as a coating composition. The coating composition can include at least the at least one API from the aqueous formulation. Alternatively, the coating composition can include a portion of the at least one excipient from the aqueous formulation, a portion of the solvent (water and optional co-solvents) from the aqueous formulation, or some combination thereof. The content of the coating composition on the coated microneedle array can depend at least in part on the aqueous formulation, the method of coating the microneedle array, the number of contacting steps, other optional steps, length and quantities of delays between contacting steps, the speed of withdrawal from the reservoir, other factors not discussed herein, or some combination thereof.

[0074] A microneedle array includes microneedles affixed to a substrate. At least a portion of the composition is present as a coating on at least a portion of the microneedles. That is, at least a portion of the composition is not present on the substrate of the microneedle array. In one embodiment, at least 50% by weight of the composition is present on the microneedles. In one embodiment, at least 75% by weight of the composition is present on the microneedles. In one embodiment, at least 90% by weight of the composition is present on the microneedles.

EXAMPLES SECTION

Example 1 - PTH/Zn

[0075] A coating formulation was prepared consisting of 7.45% rhPTH(1-34), (available from

Bachem, Bubendorf, Switzerland), zinc chloride (0.19%), hydroxyethylcellulose 100 mPa·s (100 cP) solution (2.07%), sucrose (39.88%), and water for injection (50.41%). Solid microneedle arrays made of liquid crystal polymer were prepared as described in U.S. Patent No. 9,339,956. The arrays were 12.7 mm in diameter and had 316 square pyramidal needles with a height of 500 microns and tip to tip spacing of 550 microns. The arrays were dipped into the coating formulation to prepare tip-coated arrays as described in U.S. Patent No. 8,741,377. The coated arrays were analyzed for rhPTH(1-34) content by HPLC and had an average content of 93 mcg (n=6). sMTS patches were prepared by attaching the array to an adhesive overlay with a diameter of 27 mm.

[0076] Animal testing was performed with young, naïve, adult female mixed breed agricultural swine (Yorkshire X) with minimal skin pigmentation. The animals weighed approximately 22 to 30 kilograms at dosing. All animals were anesthetized prior to patch application. The test site (ham) was prepared by clipping, shaving, and scrubbing with a 3M Buf Puf and soapy water. Finally the test site was cleaned with a gauze pad soaked in 70% isopropyl alcohol solution and allowed to dry for at least 2 minutes prior to patch application. A single sMTS patch was applied to the test site at time 0. The patches remained on the skin for 15 minutes before removal. The skin surface was swabbed after patch removal and residual rhPTH left on the skin surface was determined by HPLC. Residual rhPTH on the post-application patch was also determined by HPLC. The difference between the initial content and the residual left on the skin and patch was used to determine a net delivered dose of 66 µg.

[0077] Blood draws (1.5 mL per time point) were taken from an ear vein at times 0 min (pre-application), 2 min, 5 min, 10 min, 15 min, 20 min, 30 min, 60 min, 120 min, and 180 min. Plasma sample volume was approximately 0.7 mL. Plasma was stored at -70°C prior to analysis. Plasma samples were assayed using ELISA assay kits. rhPTH (1-34) standards were run on each individual plate to determine a standard curve for that plate. The average plasma levels (n=4) normalized by Cmax are shown in FIG. 3 as a solid line.

Comparative Example 1 - PTH

[0078] A coating formulation was prepared consisting of of 7.22% rhPTH(1-34), (available from Bachem, Bubendorf, Switzerland), hydroxyethylcellulose 100 mPa·s (100 cP) solution (2.00%), sucrose (40.71%), and water for injection (50.06%). sMTS patches were prepared as described in Example 1. The coated arrays were analyzed for rhPTH(1-34) content by HPLC and had an average content of 66 µg (n=6). The net delivered dose was 56 µg. Animal testing and analysis was performed as described in Example 1 The average plasma levels (n=3) normalized by Cmax are shown in FIG. 3 as a dashed line.

Example 2 - rhGH/Zn

[0079] A coating formulation was prepared consisting of 1.3% rhGH, (available from ProSpec-Tany TechnoGene Ltd., Ness Ziona, Israel), zinc chloride (0.014%), hydroxyethylcellulose 100 mPa·s (100 cP) solution (2.4%), sucrose (39.85%), and water for injection (56.4%). Solid microneedle arrays made of liquid crystal polymer were prepared as described in U.S. Patent No. 9,339,956. The arrays were 12.7 mm in diameter and had 316 square pyramidal needles with a height of 500 microns and tip to tip spacing of 550 microns. The arrays were dipped into the coating formulation to prepare tip-coated arrays as described in U.S. Patent No. 8,741,377. The coated arrays were analyzed for rhGH content by HPLC and had an average content of 1.8 µg (n=6). Six patches were applied as a single dose to each swine for a total dose of 10.5 µg. sMTS patches were prepared by attaching the array to an adhesive overlay with a diameter of 27 mm.

[0080] Animal testing was performed with young, naive, adult female mixed breed agricultural swine (Yorkshire X) with minimal skin pigmentation. The animals weighed approximately 22 to 30 kilograms at dosing. All animals were anesthetized prior to patch application. The test sites (ham) were prepared by clipping, shaving, and scrubbing with a 3M Buf Puf and soapy water. Finally the test sites were cleaned with a gauze pad soaked in 70% isopropyl alcohol solution and allowed to dry for at least 2 minutes prior to patch application. A single sMTS patch was applied to each of six test sites at time 0. The patches remained on the skin for 30 minutes before removal. The skin surface was swabbed after patch removal and residual rhPTH left on the skin surface was determined by HPLC. Residual rhPTH on the post-application patch was also determined by HPLC. The difference between the initial content and the residual left on the skin and patch was used to determine a net delivered dose of 10.0 µg.

[0081] Blood draws (1.5 mL per time point) were taken from an ear vein at times 0 min (pre-application), 10 min, 20 min, 30 min, 40 min, 50 min, 60 min, 90 min, 120 min, 180 min, 300 min, and 420 min. Plasma sample volume was approximately 0.7 mL. Plasma was stored at -70°C prior to analysis. Plasma samples were assayed using ELISA assay kits. rhGH (1-34) standards were run on each individual plate to determine a standard curve for that plate. The average plasma levels (n=4) normalized by Cmax are shown in FIG. B4 as a solid line.

Comparative Example 1 - rhGH

[0082] A coating formulation was prepared consisting of 1.3% rhGH, (available from ProSpec-Tany TechnoGene Ltd., Ness Ziona, Israel), hydroxyethylcellulose 100 mPa·s (100 cP) solution (2.3%), sucrose (40.0%), and water for injection (56.5%). sMTS patches were prepared as described in Example 2. The coated arrays were analyzed for rhGH content by HPLC and had an average content of 1.8 µg (n=6). Six patches were applied as a single dose to each swine for a total dose of 11.0 µg. The net delivered dose was 10.7 µg. Animal testing and analysis was performed as described in Example 1. The average plasma levels (n=4) normalized by Cmax are shown in FIG. 4 as a dashed line.

[0083] Various embodiments of **ZINC COMPOSITIONS FOR COATED MICRONEEDLE**

ARRAYS are disclosed. One skilled in the art will appreciate that the present disclosure can be practiced with embodiments other than those disclosed. The disclosed embodiments are presented for purposes of illustration and not limitation, and the present disclosure is limited only by the claims that follow.

REFERENCES CITED IN THE DESCRIPTION

Cited references

This list of references cited by the applicant is for the reader's convenience only. It does not form part of the European patent document. Even though great care has been taken in compiling the references, errors or omissions cannot be excluded and the EPO disclaims all liability in this regard.

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- US20090016935A1 **[0006]**
- US20040049150 **[0025]**
- US20040265354 **[0025]**
- US20060195067A **[0025]**
- US20050261631 **[0067]**
- US6881203B **[0067]**
- US61168268 **[0067]**
- US61115840 **[0067]**
- US9339956B **[0075]** **[0079]**
- US8741377B **[0075]** **[0079]**

Patentkrav

1. Medicinsk indretning omfattende:

en sammensætning omfattende en terapeutisk aktiv mængde af et aktivt middel og en zinkforbindelse valgt fra gruppen bestående af zink, farmaceutisk acceptable salte af zink, og blandinger deraf; og

en anordning af mikronåle;

hvor mindst en del af sammensætningen er til stede som belægning på mindst en del af mikronålene; og hvor zinkforbindelsen omfatter et uorganisk salt af zink; og hvor det aktive middel er et protein eller et peptid.

2. Medicinsk indretning ifølge krav 1, hvor zinkforbindelsen omfatter et divalent salt af zink.

3. Medicinsk indretning ifølge et hvilket som helst foregående krav, hvor zinkforbindelsen omfatter zinkchlorid.

4. Medicinsk indretning ifølge et hvilket som helst foregående krav, hvor molforholdet mellem zinkforbindelse og aktivt middel er 0,1 til 2,0.

5. Medicinsk indretning ifølge et hvilket som helst foregående krav, hvor molforholdet mellem zinkforbindelse og aktivt middel er 0,2 til 1,5.

6. Medicinsk indretning ifølge et hvilket som helst foregående krav, hvor mængden af zinkforbindelse er 1% til 8% af den samlede vægt af sammensætningen.

7. Medicinsk indretning ifølge et hvilket som helst foregående krav, hvor mængden af zinkforbindelse er 2% til 6% af den samlede vægt af sammensætningen.

8. Medicinsk indretning ifølge et hvilket som helst af kravene 1 til 7, hvor det aktive middel er valgt fra gruppen bestående af humant væksthormon (hGH), vævsplasminogenaktivator (TPA), calcitoningen-relateret peptid (CGRP),

luteiniserende hormon frigivende hormon (LHRH), goserelin, leuprolid, buserelin, triptorelin, gonadorelin, napfarelin, menotropiner, follikel stimulerende hormon (FSH), luteiniserende hormon (LH), humane menopausale goanadotropiner (hMG), humant choriongonadotropin (hCG), vasopressin, desmopressin, insulin, adrenokortiokotropt hormon (ACTH), ACTH (1-24), calcitonin, parathyroidt hormon (PTH), parathyroide hormonantagonister, parathyroidt hormon-relateret protein (PTHrP), oxytocin, deamino [Val4, D-Arg8] argininvasopressin, interferon-alpha, interferon-beta, interferon-gamma, tumornekrosefactor (TNF), erythropoietin (EPO), granulocytmakrofagkoloni stimulerende faktor (GM-CSF), granulocytkoloni stimulerende faktor (G-CSF), interleukiner, interleukin-2 [[IL-2]] (IL-2), interleukin-10 (IL-10), glucagon og væksthormon frigivende faktor (GRF).

9. Medicinsk indretning ifølge et hvilket som helst foregående krav, hvor mere end 50 vægtprocent af sammensætningen er til stede som en belægning på mikronålene.

10. Medicinsk indretning ifølge et hvilket som helst foregående krav, hvor mere end 75 vægtprocent af sammensætningen er til stede som en belægning på mikronålene.

11. Medicinsk indretning ifølge et hvilket som helst foregående krav, hvor mere end 90 vægtprocent af sammensætningen er til stede som en belægning på mikronålene.

12. Sammensætning som defineret i et hvilket som helst foregående krav til anvendelse som et medikament i en indretning ifølge et hvilket som helst foregående krav, hvor nævnte sammensætning skal leveres til et pattedyr ved anvendelse af nævnte indretning på en hudoverflade af pattedyret, hvilket gør det muligt for indretningen at forblive i berøring med huden i en tidsperiode for at lade en del af det aktive middel blive overført til huden af pattedyret, og efterfølgende at fjerne indretningen fra pattedyret.

13. Sammensætning til anvendelse ifølge krav 12, hvor Cmax'et opnået hos pattedyret er større end Cmax'et, som ville blive opnået, hvis en lignende indretning med en sammensætning uden zinkforbindelse blev anvendt på

pattedyret i tidsperioden.

14. Sammensætning til anvendelse ifølge kravene 12 eller 13, hvor AUC'en opnået hos pattedyret er større end AUC'en, som ville blive opnået, hvis en lignende indretning med en sammensætning uden zinkforbindelse blev anvendt på pattedyret i tidsperioden.

DRAWINGS

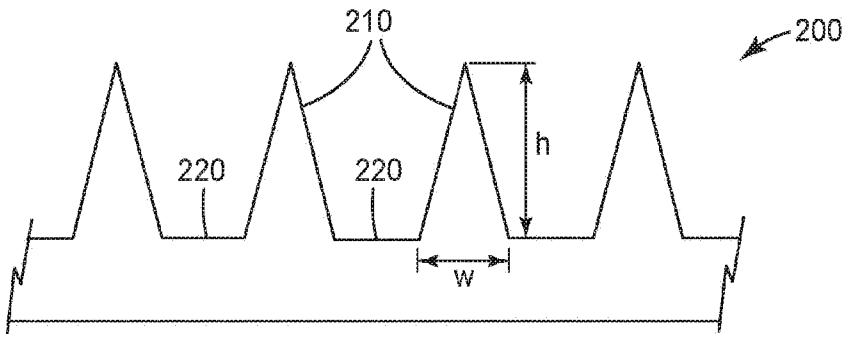

FIG. 1

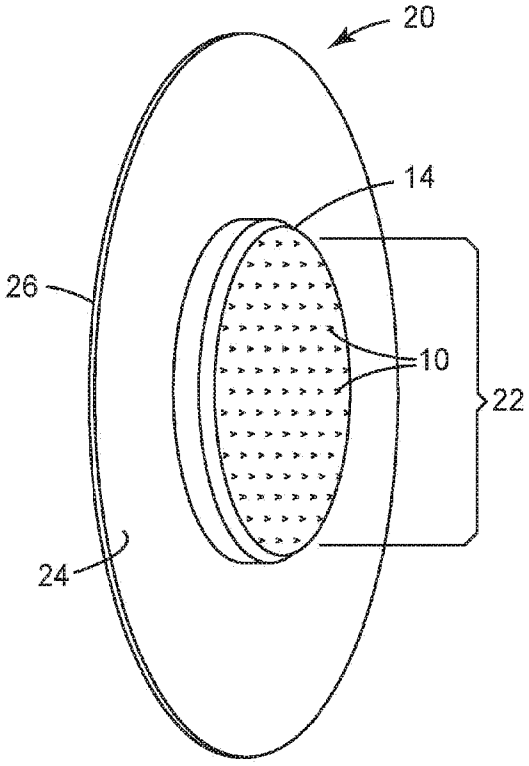

FIG. 2

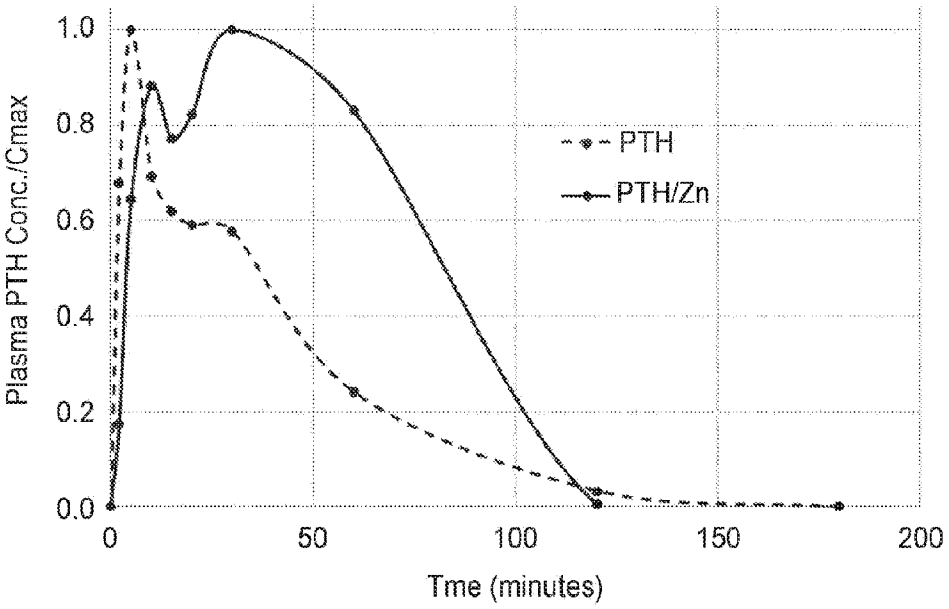
Plasma PTH Conc./Cmax
1.0
0.8
0.6
0.4
0.2
0.0
0
50
100
150
200
Tme (minutes)
PTH
PTH/Zn

FIG. 3

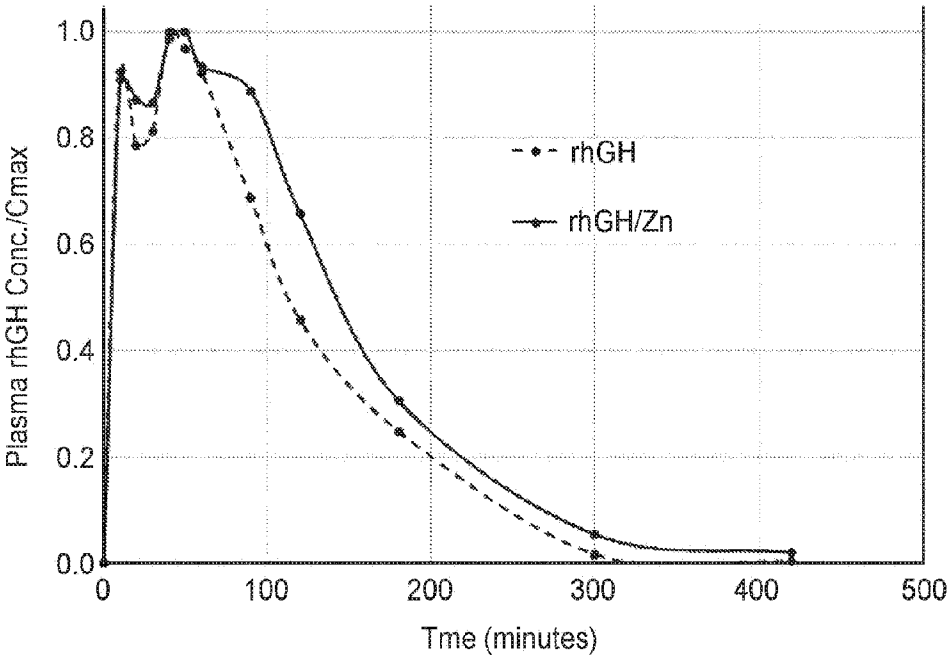
Plasma rhGH Conc./Cmax
1.0
0.8
0.6
0.4
0.2
0.0
0
100
200
300
400
500
Tme (minutes)
rhGH
rhGH/Zn

FIG. 4