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(54) Title: NUTRITIONAL AND THERAPEUTIC MUCOADHESIVE FORMULATIONS

(57) Abstract: A supplement formulation, comprising a mucoadhesive and an effective amount of one or more of a medicinal food or a nutritional supplement is described as well as use for the delivery of same to mucosal surfaces. The supplement formulation may be in the form of a liquid or gel.

NUTRITIONAL AND THERAPEUTIC MUCOADHESIVE FORMULATIONS

CROSS REFERENCE TO RELATED APPLICATION

[0001] This application claims priority under 36 U.S.C. § 119(e) to U.S. Provisional Patent Application No. 61/941,268, filed February 18, 2014, the content of which is hereby incorporated by reference in its entirety.

TECHNICAL FIELD

[0002] The present disclosure relates to viscous mucoadhesive formulations useful in the delivery of nutritional and medicinal supplements.

BACKGROUND

[0003] Mucous membranes provide a protective layer on the surface of several body cavities, such as the oral cavity, the nasal cavity, the gastrointestinal and respiratory tracts, the vagina, and the bladder. Cells within or glands adjacent to these membranes secrete mucus, a fluid or gel primarily composed of water, lipids, inorganic salts and mucin glycoproteins, which serve to form a protective barrier to inhibit passage of harmful materials to the underlying tissue. There are several diseases and disorders of these mucosal surfaces which can result in severe pain, irritation, erythema, and/or ulceration. Examples of such diseases in the oral cavity include aphthous ulcers, bullous pemphigoid, oral lichen planus, and oral mucous membrane contact dermatitis (1,2); examples of diseases of the nasal mucous membrane include sinusitis and rhinitis (3); an example for the bladder is interstitial cystitis (4). Certain diseases such as Behçet syndrome can affect the mucocutaneous membranes of several regions of the body (5). Many other ulcerative mucocutaneous diseases are known. Acid reflux from the stomach, especially the frequent occurrence of reflux known as gastroesophageal reflux disease (GERD) can result in erythema, pain, and erosion of the lining of the esophagus (6). Diseases of the lower gastrointestinal (GI) tract can have manifestations in the upper GI tracts, for example inflammatory bowel disease (7). There are also painful ulcerative disorders of mucosal surfaces which result as an adverse side-effect in certain therapies, such as chemotherapy and radiation therapy (8). Examples of such side-effects include mucositis, esophagitis, and radiation proctitis.

[0004] Thus, a need exists in the art for effective and safe therapies that target mucous membranes. This disclosure satisfies this need and provides related advantages as well.

SUMMARY

[0005] Viscous, mucoadhesive liquid formulations used for the prevention and treatment of mucosal disorders were previously described in U.S. Patent Nos. 7,544,348 and 7,547,433. These formulations described the use of such liquids either without any pharmacologically-active ingredient or with a pharmacologically-active ingredient. Without being bound by theory, the Applicants believe that the liquids were effective without a pharmaceutical by virtue of the fact that the formulation components and entrapped water remained in place on the mucosa for an extended period providing a temporary protective barrier. The medical benefits of the viscous mucoadhesive liquid could be enhanced by inclusion of certain pharmaceutical agents in the formulation. Additionally, the viscous mucoadhesive liquid was found to act as a drug delivery vehicle as the pharmaceutical agent was held in place on the mucosa for a longer duration than was the case for a liquid formulation which was not both mucoadhesive and viscous. Longer retention of the pharmaceutical on the mucosal surface coupled with possible drug transport-enabling interactions between the liquid components and the mucin coating and/or epithelial cells lining the mucosa enabled more of the drug to reach the systemic circulation rapidly by crossing the mucosa and entering the bloodstream.

[0006] However, neither U.S. Patent No. 7,544,348 nor U.S. Patent No. 7,547,433 disclose that the viscous mucoadhesive liquid formulations described therein could be used beneficially in conjunction with compounds and mixtures of compounds that had no intrinsic pharmacological action, but were medically beneficial. It was a surprising finding that combining the viscous mucoadhesive liquid formulations with medical foods and/or nutritional supplements provided added medical benefits compared with either alone. Accordingly, this disclosure provides mucoadhesive formulations which contain medical foods and/or nutritional supplements in which primary beneficial medical effect is provided by either the medical food/ nutritional supplement or the viscous mucoadhesive formulation. In either case, the other component provides an additional or additive medical effect. Furthermore, the disclosed formulations unexpectedly improve the delivery of the medical food/nutritional supplement to the location where it is medically effective; either the mucosal surface, or aiding more rapid transit and/or transit of greater amounts of the dose to the bloodstream. To the best of Applicant's knowledge, such uses of viscous mucoadhesive

formulations in combination with medical foods and/or nutritional supplements has not been previously reported. The mucoadhesive formulations of this invention can be viscous liquids or gels.

[0007] In another aspect, also provided are viscous mucoadhesive formulations comprising nanoparticles containing one or more of a pharmacologically-active component, a medical food, or a nutritional supplement, or some combination of pharmacologically-active components, medical foods, and nutritional supplements. The combined nanoparticle and viscous mucoadhesive liquid formulation provide improved delivery of the active components to the sites in the body required for effectiveness of these active components. The nanoparticles can be optionally coated with a targeting group, such as folic acid, biotin or B vitamins, such as vitamin B12.

[0008] In another aspect, provided is one or more of a nanoparticle, a pharmacologically-active component, a medical food, or a nutritional supplement, covalently linked to a targeting group (targeted conjugates) and formulated in a viscous mucoadhesive formulation for the purpose of improving the delivery of the pharmacologically-active component, medical food, or nutritional supplement to the sites in the body required for effectiveness of these active components.

[0009] The viscous, mucoadhesive formulations containing the one or more medical foods and/or nutritional supplements are to be used for the prevention and treatment of mucocutaneous conditions and/or other disorders. Considering the primary purpose of each component separately, the viscous, mucoadhesive and the medical food/nutritional supplement can be used to treat the same disease or condition, or different diseases or conditions in which the different diseases and conditions may be related or unrelated. Additionally, the viscous, mucoadhesive formulation can be used to improve the delivery of beneficial medical foods or nutritional supplements which may treat the same condition or different conditions. These formulations are especially beneficial in diseases and conditions in which a wide area of the mucosal surface requires treatment, but the formulations may also be used in treating small areas of the mucosal surface, or in enhancing the delivery of the medical food to the required region of the body.

[0010] In a separate embodiment, the present disclosure provides nanoparticles or targeted conjugates containing one or more nutritional supplements or medical foods and

pharmaceutical formulations thereof, for the prevention and treatment of mucocutaneous conditions and/or other disorders . In one aspect, the nanoparticles further comprise, or alternatively consist essentially of, or yet further consist of, a targeting moiety for targeted administration. Non-limiting examples of targeting moieties include one or more of folic acid, biotin or B vitamins, such as vitamin B12.

[0011] In one aspect, the present inventions provide viscous, mucoadhesive formulations or compositions containing nanoparticles that in one aspect, comprise targeted conjugates to be used for the prevention and treatment of mucocutaneous conditions and/or other disorders. Considering the primary purpose of each component separately, the viscous, mucoadhesive and the nanoparticles or targeted conjugates can be used to treat the same disease or condition, or different diseases or conditions in which the different diseases and conditions may be related or unrelated. Additionally, the viscous, mucoadhesive formulation can be used to improve the delivery of nanoparticles or targeted conjugates which may treat the same condition or different conditions. These formulations are especially beneficial in diseases and conditions in which a wide area of the mucosal surface requires treatment, but the formulations may also be used in treating small areas of the mucosal surface, or in enhancing the delivery of the medical food to the required region of the body.

[0012] In order that mucocutaneous disorders are treated effectively, the viscous mucoadhesive formulation should be in contact with the lesion for the period of time required to derive benefit. To grant such benefit, this disclosure describes mucoadhesive, viscous formulations containing one or more of a medical food, nutritional supplement, nanoparticle or targeted conjugate. The gel or liquid formulation(s) can readily be applied to the affected region of the mucosa by methods known in the art, while the high viscosity and mucoadhesion will cause the gel or liquid to remain in contact with the lesion for extended periods. The formulations of the present invention cab be applied to treat mucocutaneous lesions in a variety of body compartments, including, but not limited to, the oral cavity, the nasal cavity, the esophagus, the rectum, the bladder, and the vagina.

[0013] Furthermore, the viscous, mucoadhesive formulations of the current disclosure can be used to deliver one or more medical foods and/or nutritional supplements to the mucosal surface, either for the prevention or treatment of diseases and disorders of the mucosa, or for rapid delivery of the part of medical food/nutritional supplement component to the systemic circulation by transfer through the mucosa.

[0014] Furthermore, the viscous, mucoadhesive formulations as disclosed herein can be used to deliver one or more nanoparticles and/or targeted conjugates to the mucosal surface, either for the prevention or treatment of diseases and disorders of the mucosa, or for rapid delivery of the nanoparticle and/or targeted conjugate component to the systemic circulation by transfer through the mucosa.

[0015] In another aspect of this disclosure, the viscous mucoadhesive formulations contain one or more medical foods and/or nutritional supplements, and one or more pharmacologically-active agents (pharmaceutical active ingredients) to provide an increased medically beneficial effect.

[0016] In another aspect of this disclosure, the viscous mucoadhesive formulations contain one or more type of nanoparticle and/or targeted conjugate as well as one or more pharmacologically-active agents (pharmaceutical active ingredients) to provide an increased medically beneficial effect.

DETAILED DESCRIPTION

Definitions

[0017] All technical and patent publications cited herein are incorporated herein by reference in their entirety. Throughout this disclosure, some citations are referenced by an Arabic numeral, the complete citation of which is provided at the end of the specification. All references are incorporated by reference herein to more fully describe the state of the art to which this disclosure pertains.

[0018] All numerical designations, *e.g.*, pH, temperature, time, concentration, and molecular weight, including ranges, are approximations which are varied (+) or (-) by increments of 0.1 or 1.0, as appropriate. It is to be understood, although not always explicitly stated that all numerical designations are preceded by the term "about". It also is to be understood, although not always explicitly stated, that the reagents described herein are merely exemplary and that equivalents of such are known in the art.

[0019] As used in the specification and claims, the singular form "a", "an" and "the" include plural references unless the context clearly dictates otherwise.

[0020] "Comprising" refers to compounds, compositions and methods including the recited elements, but not excluding others. "Consisting essentially of," when used to define

compounds, compositions or methods, shall mean excluding other elements that would materially affect the basic and novel characteristics of the claimed technology. "Consisting of," shall mean excluding any element, step, or ingredient not specified in the claim. Embodiments defined by each of these transition terms are within the scope of this disclosure.

[0021] As used herein, "nanoparticle", "nanocarrier", or "nanostructure" refers to a microscopic particle less than about 1 micron in diameter. In some embodiments, the nanoparticles range in size from about 1 nm to about 1,000 nm in diameter, or alternatively between about 10 nm to about 1000 nm, or alternatively between about 10 nm to about 900 nm, or alternatively between about 10 nm to about 800 nm, or alternatively between about 10 nm to about 700 nm, or alternatively between about 10 nm to about 600 nm, or alternatively between about 10 nm to about 500 nm, or alternatively between about 20 nm to about 1000, or alternatively between about 20 nm to about 800 nm, or alternatively between about 20 nm to about 700 nm, or alternatively between about 20 nm to about 600 nm, or alternatively between about 20 nm to about 500 nm; or alternatively between about 30 nm to about 1000 nm, or alternatively between about 30 nm to about 900 nm, or alternatively between about 30 nm to about 800 nm, or alternatively between about 30 nm to about 700 nm, or alternatively between about 100 nm to about 900 nm, or alternatively between about 200 nm to about 1000 nm, or alternatively between about 300 nm to about 1000 nm, or alternatively between about 400 nm to about 1000 nm, or alternatively between about 500 nm to about 1000 nm; or alternatively between about 600 nm to about 1000 nm; or alternatively between about 700 nm to about 1000 nm; or alternatively between about 800 nm to about 1000 nm; or alternatively between about 900 nm to about 1000 nm; or alternatively between about 100 nm to about 300 nm; or alternatively between about 200 nm to about 600 nm; or alternatively between about 300 nm to about 600 nm; or alternatively between about 500 nm to about 800 nm.

[0022] As used herein, "polymer" refers to a naturally-occurring, synthetic or semi-synthetic large molecule (macromolecule) typically composed of repeating structural units connected by covalent chemical bonds. Polymers useful for the implementation of this disclosure have molecular weights in the range of 1 to 5000 kDa. The polymers can be stable, degradable and made of random copolymers or block copolymers.

[0023] As used herein, "random copolymer" refers to a polymer comprising two or more repeating structural units in which the sequence of the individual repeating structural units is random and not predetermined or defined.

[0024] As used herein, "block copolymer" refers to a polymer comprising two or more repeating structural units in which individual repeating structural units are connected to each other forming identifiable blocks of repeating structural units within the complete polymer strand.

[0025] As used herein, "charged group" refers to a chemical functional group that is fully ionized resulting in that group having either a positive or a negative charge, or possibly multiple positive or multiple negative charges. Polymers could have multiple charged groups either as components of the polymer chain, and/or as attachments to the polymer, either direct attachment or by way of a linker. Polymer charged groups may be either naturally-occurring or synthetic. A charged group may be part of a therapeutically active compound, either as an intrinsic component of that compound or as a synthetic analog of the therapeutically active compound, for example, a prodrug.

[0026] As used herein, "ionisable group" refers to a chemical functional group that is partially ionized at or close to physiological pH resulting in that group having either a partial positive or a partial negative charge. The charge of an ionisable group will vary with pH. Polymers could have multiple ionisable groups either as components of the polymer chain, and/or as attachments to the polymer, either direct attachment or by way of a linker. Polymer ionisable groups may be either naturally-occurring or synthetic. An ionisable group may be part of a therapeutically active compound, either as an intrinsic component of that compound or as a synthetic analog of the therapeutically active compound, for example, a prodrug.

[0027] As used herein, "polyelectrolyte complex" or "PEC" refers to a three-dimensional structure resulting from the formation of multiple ionic bonds between two or more compounds having chemical functional groups that are charged and/or ionisable wherein at least one compound possesses a net negative charge and at least one compound has a net positive charge, and at least one compound preferentially is a polymer. The diameter of PECs can typically range from 1 nm to several microns, with average particle size and particle size distribution controlled by the chemical and physical nature of the constituent components and method of preparation. PECs can be water soluble (i.e. suspension of nanoparticles in water

results in a clear, transparent liquid) or insoluble (i.e. suspension of nanoparticles in water results in a cloudy liquid). PEC nanoparticles typically can range in size from about 1 nm to about 1,000 nm in diameter, or alternatively about 5 nm to about 400 nm, or alternatively about 10 nm to about 300 nm.

[0028] As used herein, the term "carrier" encompasses any of the standard carriers, such as a phosphate buffered saline solution, buffers, water, and emulsions, such as an oil/water or water/oil emulsion, and various types of wetting agents. The carrier also can include stabilizers and preservatives. In one aspect of the invention, the carrier is a buffered solution such as, but not limited to, a PCR buffer solution, a phosphate buffered saline solution, or another pharmaceutically acceptable carrier.

[0029] As used herein, the term "covalently linked to a targeting group" intends linking a targeting group such as a B vitamin (e.g., vitamin B12) by using chemical interactions to link the amino group to an available function group (e.g., a free carboxyl group) as described herein.

[0030] As used herein, "degradable polymer" refers to a polymer which can be broken down under specific conditions to smaller units. In one aspect, repeated degradation of the polymer units in situ (in the body) allows for small fragments to be excreted or otherwise eliminated. Non-limiting examples of such include, polyesters such as PLGA, polyacetals, polyanhydrides, peptides and other polyamino acids, and block copolymers in which stable oligomers are linked by degradable linkers.

[0031] As used herein, "stable polymer" refers to a polymer in which the main structure (backbone) of the polymer cannot be broken under conditions typically found in the body. In a stable polymer, it remains possible that functional groups attached to the polymer backbone can be modified or degraded under conditions typically found in the body. Non-limiting examples of such include, polyethers such as PEG, polyacrylates, and polymethacrylates.

[0032] As used herein, "alkyl" refers to a saturated (containing no multiple carbon-carbon bonds) aliphatic (containing no delocalized π-electron system) hydrocarbon containing, if otherwise unsubstituted, only carbon and hydrogen atoms. The designation (n1C– n2C)alkyl, wherein n1 and n2 are integers from 1 to 6, refers to straight or branched chain alkyl groups comprising from n1 to and including n2 carbon atoms. An alkyl group herein may be

optionally substituted with one or more entities selected from the group consisting of halo, hydroxy, alkoxy, aryloxy, carbonyl, nitro, cyano, carboxyl and alkoxycarbonyl.

[0033] As used herein, "linker" refers to a group of atoms that is used to couple a polymeric backbone to another function or group to spatially separate the two entities. Thus, a linker of this disclosure has an essentially longitudinal axis, that is, it is essentially linear rather than highly branched or clumped, although the structure will, of course, not be exactly linear due to the angular constraints placed on the structure by required bond angles between covalently bonded atoms. Examples of linkers include, but are not limited to, straight and branched alkyl and alkenyl groups containing functional groups such as carboxyl, amino, hydroxyl, and thiol, through which covalent bonds can be formed to connect the linker to the polymer and to other components. A preferred linker is a short peptide chain (H-[NHCHR-CO]n-OH) where n is 1-20, or alternatively from 1-18, or alternatively from 1-16, or alternatively from 1-14, or alternatively from 1-12, or alternatively from 2-14, or alternatively from 2-12, or alternatively from 3-20, or alternatively from 4-18, or alternatively from 5-20, or alternatively from 5-18, and R is the same or different for each of the n amino acids, and is one of the 22 side groups known to be present in natural amino acids, wherein the linker is the same or different and is selected from the group of a short peptide chain (H-[NHCHR-CO]n-OH) where n is 1-20 and R is the same or different for each of the n amino acids, and is one of the 22 side groups known to be present in natural amino acids; a short alkyl chain $(CH_2)_n$ where n = 2-10, terminated by two amino groups or two carboxyl groups or one amino group and one carboxyl group; an oligoethyleneoxy chain $(CH_2CH_2O)_n$ where n = 2-100, terminated by two amino groups or two carboxyl groups or one amino group and one carboxyl group; a poly(lactic-co-glycolic acid) (PLGA), polylactic acid (PLA), a polyglycolic acid (PGA) chain of average molecular weight of 2 kDa to 70 kDa terminated by two amino groups or two carboxyl groups or one amino group and one carboxyl group; $-C(O)NH(CH_2)_6NH-$; $-C(O)NH(CH_2)_6NHC(O)CH_2-$; $-C(O)NH(CH_2CH_2O)_2CH_2CH_2NH-$; $-C(O)NH(CH_2CH_2O)_2CH_2CH_2NHC(O)CH_2[OCH_2CH_2]_{23}NH-$ or any combination thereof. A peptide linker can be incorporated into the polymer compound by one of the peptide condensation reactions (producing an amide bond) that are known in the art.

[0034] As used herein, a "targeting group", "targeting agent", or "targeting moiety" refers to a small molecule, peptide, protein, antibody, antibody fragment, or other targeting agent known in the art that can be attached to a therapeutic agent to alter the biodistribution and/or

pharmacokinetics of the therapeutic agent to enhance the beneficial effect. Non-limiting examples of such targeting moieties include vitamin B12, folate, biotin, peptides (e.g. RGD), antibodies, or other targeting agents known in the art.

[0035] As used herein, “therapeutic agent” refers to a compound, mixture of compounds, or biologic agent that can provide a beneficial effect when administered to a patient.

[0036] As used herein, “pharmaceutical agent”, “pharmaceutically-active agent”, and “pharmaceutically-active compound” refer to a compound, mixture of compounds, or biologic agent, such as an antibody or fragment thereof, that can provide a beneficial effect through a pharmacological mode of action when administered to a patient.

[0037] As used herein, "medical food” refers to a food that has been specially formulated and intended for the dietary management of a disease that has distinctive nutritional needs that cannot be met by normal diet alone.

[0038] As used herein, “nutritional supplement” refers to a compound, mixture of compounds, or biologic agent that is required by a living organism to survive and grow and that may otherwise not be consumed in sufficient quantities.

[0039] As used herein, a “supplement formulation” or “formulation” is a mixture of components containing one or more nutritional supplements and/or medical foods provided in a viscous mucoadhesive liquid or mucoadhesive gel carrier suitable for administration to patients. The nutritional supplements and/or medical foods can be formulated as dispersions, suspensions, dissolved ingredients, within nanoparticles, within targeted nanoparticles, or as targeted conjugates and dispersed in the liquid or gel carrier. The "supplement formulation" or “formulation” may optionally contain pharmaceutically-active agents formulated in the liquid or gel carrier, and/or pharmaceutically-active agents formulated in nanoparticles, targeted nanoparticles, and/or targeted conjugates dispersed in the liquid or gel carrier. Additional components can include one or more pharmaceutically-acceptable excipients. The "supplement formulation" or "formulation" can be comprised of a single formulation for administration to a patient or comprised of two or more formulations that are brought together and mixed immediately prior to administration to a patient.

[0040] As used herein, a “disease” or “medical condition” is an abnormal condition of an organism that impairs bodily functions, associated with specific symptoms and signs.

[0041] As used herein, the term "cancer" refers to various types of malignant neoplasms, most of which can invade surrounding tissues, and may metastasize to different sites, as defined by Stedman's Medical Dictionary, 25th edition (Hensyl ed. 1990). Examples, without limitation, of cancers which may be treated using the compounds of the present disclosure include, but are not limited to, brain, ovarian, colon, prostate, kidney, bladder, breast, lung, oral, skin and blood cancers.

[0042] As used herein, the terms "treat", "treating" and "treatment" refer to a method of alleviating or abrogating a disease and/or its attendant symptoms. The effect may be prophylactic in terms of completely or partially preventing a disorder or sign or symptom thereof, and/or may be therapeutic in terms of a partial or complete cure for a disorder and/or adverse effect attributable to the disorder. For example, the life expectancy of an individual affected with a cancer will be increased and/or that one or more of the symptoms of the disease will be reduced.

[0043] As used herein, "administer," "administering" or "administration" refers to the delivery of a nutritional supplement and/or medical foods or the formulation containing the nutritional supplement and/or medical food to a patient in a manner suitable for the treatment of a particular disease or condition. “Administration” can be effected in one dose, continuously or intermittently throughout the course of treatment. Methods of determining the most effective means and dosage of administration are known to those of skill in the art and will vary with the composition used for therapy, the purpose of the therapy, the condition being treated, and the subject being treated. Single or multiple administrations can be carried out with the formulation or dose level and pattern being selected by the treating physician. Suitable dosage formulations and/or routes of administration are known in the art and will vary with the formulation used for treatment, the purpose of the treatment, the health condition or disease stage of the subject being treated and target cell or tissue. Non-limiting examples of route of administration include oral administration, vaginal, rectal, nasal administration, injection, and topical application.

[0044] A "patient" or a “subject” refers to any higher organism that is susceptible to disease. Examples of such higher organisms include, without limitation, mice, rats, rabbits, dogs, cats, horses, cows, pigs, sheep, fish and reptiles. In some embodiments, "patient" or “subject” refers to a human being.

[0045] As used herein, the term "an effective amount" refers to that amount of the nutritional supplement and/or medical food as described herein, which has the effect of (a) preventing a disorder from occurring in a subject that may be predisposed to a disorder, but may have not yet been diagnosed as having it; (b) inhibiting a disorder, i.e., arresting its development; or (c) relieving or ameliorating the disorder or the symptoms of the disorder. For example when the disease or condition is cancer, an effective amount intends, but is not limited to (1) reducing the size of the tumor; (2) inhibiting (that is, slowing to some extent, preferably stopping) tumor metastasis; (3) inhibiting to some extent (that is slowing to some extent, preferably stopping) tumor growth; (4) relieving to some extent (or preferably eliminating) one or more symptoms associated with the cancer; and/or (5) extending survival time of the patient.

[0046] As used herein, the term “mucocutaneous” area intends a mucous membrane that provides a protective layer on the surface of several body cavities, including but not limited to the oral cavity, the nasal cavity, the gastrointestinal (rectal, colon or intestinal) and respiratory tracts, the vagina, the bladder and the urinary tract.

[0047] A mucocutaneous disorder is a condition that causes discomfort to a patient or subject. Non-limiting examples of such include mucositis, Behcet's disease, apthous ulcer, bullous pemphigoid, chemical cystitis, radiation cystitis, erythema multiforme, esophagitis, interstitial cystitis, oral Lichen planus, pemphigus, radiation proctitis, or ulcerative colitis.

MODES FOR CARRYING OUT THE DISCLOSURE

Formulations and Compositions

[0048] This disclosure provides a supplement formulation comprising, or consisting essentially of, or consisting of, a mucoadhesive and an effective amount of one or more of a medicinal food or a nutritional supplement. In one aspect, the supplement formulation is a liquid. As used herein, reference to a liquid supplement intends that the formulation is capable of flowing without applied pressure and that the formulation can be applied to as large an area as possible of the target mucosal surface, or a mucosal surface that is more than 4 inches from an external orifice. In another aspect, the supplement is a gel. As used herein, a gel supplement is a formulation that is not capable of flowing without applied pressure and it is intended that the formulation be applied to a small discrete area of the mucosal surface close to an external orifice.

[0049] The FDA defines a medical food in section 5(b)(3) of the Orphan Drug Act (21 U.S.C. 360ee(b)(3)). It is described as "a food which is formulated to be consumed or administered enterally under the supervision of a physician and which is intended for the specific dietary management of a disease or condition for which distinctive nutritional requirements, based on recognized scientific principles, are established by medical evaluation." Nutritional supplements do not fall under this definition solely because of the fact that no claims can be made regarding their use for preventing or treating specific diseases or broad categories of disease. For the purpose of this disclosure, nutritional supplements are considered different from medical foods, but the scope of this disclosure includes either medical foods, nutritional supplements, or combinations of both incorporated in viscous mucoadhesive formulations to provide a beneficial medical effect. The formulations are liquids or gels.

[0050] In one aspect, the viscous, mucoadhesive formulations of the current disclosure contain one or more medical foods. A medical food component is an ingredient which the FDA has determined can be used in formulations as a major treatment modality.

[0051] The medical foods which can be formulated with the viscous, mucoadhesive formulations include, but are not limited to acetylcarnitine, acetylcholine, arginine, caprylic triglyceride, choline, cinnamon, cocoa, cyanocobalamin, dextrose, folic acid, GABA (4-aminobutanoic acid), ginkgo biloba, glutamic acid, glutamine, grape seed extract, griffonia extract, histidine, hydrolyzed whey protein, 5-hydroxytryptophan, methylcobalamin, pyridoxine, valerian extract, and serine. Other medical foods that can be formulated with the viscous, mucoadhesive formulations will be known to those skilled in the art.

[0052] In another aspect, the viscous, mucoadhesive formulations of the current invention contain one or more nutritional supplements. A nutritional supplement component is an ingredient which the FDA has determined can be used in formulations but no claims can be made to any major treatment modality.

[0053] Nutritional supplements which can be formulated with the viscous, mucoadhesive formulations include water-soluble vitamins such as thiamine (vitamin B1), riboflavin(vitamin B2), niacin (vitamin B3), pantothenic acid, biotin, pyridoxine (vitamin B6), folic acid, cobalamin (vitamin B12), and ascorbic acid (vitamin C). Other water-soluble

vitamins that can be formulated with the viscous, mucoadhesive formulations will be known to those skilled in the art.

[0054] Nutritional supplements which can be formulated with the viscous, mucoadhesive formulations include fat-soluble vitamins such as vitamins A, D, E, and K. Other fat-soluble vitamins that can be formulated with the viscous, mucoadhesive formulations will be known to those skilled in the art.

[0055] Nutritional supplements which can be formulated with the viscous, mucoadhesive formulations include minerals such as calcium, chromium, iron, magnesium, and zinc (in medically-acceptable oxidation states and medically-acceptable salt forms). Other minerals that can be formulated with the viscous, mucoadhesive formulations will be known to those skilled in the art.

[0056] Other nutritional supplements which can be formulated with the viscous, mucoadhesive formulations include probiotics, red yeast rice, St. John's Wort. Other nutritional supplements that can be formulated with the viscous, mucoadhesive formualations will be known to those skilled in the art.

[0057] The formulations of this disclosure can include one or more of the above-noted medical foods and/or nutritional supplements, selected for the particular condition or treatment that this subject or patient to be treated requires.

[0058] In one aspect, the medical food and/or nutritional supplement can be covalently-linked to a targeting moiety directly or by way of a suitable linker. Methods to utilize functional groups on the medical food and/or nutritional supplement molecule for the attachment of linkers and targeting groups are known to those skilled in the art.

[0059] As used herein, the term "mucoadhesive" intends that specific components of the formulation cause the entire formulation to adhere to a mucosal surface. Non-limiting examples of such include a linear or cross-linked polyacrylic acid, carboxymethylcellulose, hydroxyalkylcellulose, polyvinylpyrrolidone dextran sulfate, dermatan sulfate, hyaluronic acid, a water-soluble vinyl polymer, guar gum, xanthan gum tragacanth gum and pectin, chitosan, a linear or cross-linked polymer polyanionic or polycationic polymer which may or may not already be known to provide mucoadhesion. The formulations of this disclosure can contain a single mucoadhesive component or mixtures thereof. In one aspect, the mucoadhesives are cross-linked homopolymers and copolymers based on acrylic acid and

methacrylic acid, especially the Carbopol® and polycarbophil polymers and Eudragit polymers supplied by Rohm-Haas; most preferred are Carbopol®, Noveon AA1, and Eudragit L-100.

[0060] In one aspect, the mucoadhesive is a commercially available Carbopol® polymer (Lubrizol). Lubrizol is described these polymers as rheology modifiers. Most Carbopol® polymers are high molecular weight homo- and copolymers of acrylic acid cross-linked with a polyalkenyl polyether. Specific examples of such include a carboxyvinyly polymer commercially available as Carbopol®971P (also known as Carbomer Homopolymer Type A (USP/NF) or as a Carbomer (European Ph. Eur.) or as carboxypolymethylene). It is commercially available at a viscosity of about cP (25°C) of about 4,000-11,000 when tested on a Brookfield RVT, 20 rpm, neutralized to pH at 7.3 to 7.8.

[0061] In the formulation, a mucoadhesive is generally at a concentration between about 0.5 w/w % and about 30.0 w/w %, or alternatively between about 0.5% to about 20%, or alternatively from about 1.0% to about 20%, or alternatively from about 1.0% to about 15%, or alternatively from about 1.0% to about 10%, or alternatively from about 1.0% to about 5%, or alternatively from about 1.0 % to about 3%, or alternatively from about 1.5% to about 20%, or alternatively from about 1.5% to about 20%, or alternatively from about 1.5% to about 15%, or alternatively from about 1.5% to about 10%, or alternatively from about 1.5% to about 5%, or alternatively from about 1.5 % to about 3% , or alternatively about 3% (all values given in w/w%).

[0062] In one aspect, the mucoadhesive of the present disclosure will contain cross-linked polyacrylic acid hydrogels plus optional linear polyacrylate and/or polymethacrylate and/or linear copolymers derived from acrylate and methacrylate monomers. Useable viscosity-inducing agents are many and include agar, bentonite, glycerin, providone, kaolin, tragacanth, sodium alginate and cross-linked polyacrylic acids. The final pH of the formulation is between about 6.0 to about 10, or alternatively from about 6.5 to about 9.5.

[0063] The formulation comprising, or alternatively consisting essentially of, or yet further consisting of, one or more medicinal food and/or nutritional supplement will vary with the intended use, discussed in more detail below. For example, the nutritional supplement and/or medicinal food is present in the supplement in an amount from about 0.00001 % w/w to about 10% w/w, or alternatively from about 0.0001 % w/w to about 10% w/w, or

alternatively from about 0.001 % w/w to about 10% w/w, or alternatively from about 0.01 % w/w to about 10% w/w, or alternatively from about 0.1 % w/w to about 10% w/w, or alternatively from about 0.00001 % w/w to about 5% w/w, or alternatively from about 0.0001 % w/w to about 5% w/w, or alternatively from about 0.001 % w/w to about 5% w/w, or alternatively from about 0.01 % w/w to about 5% w/w, or alternatively from about 0.1 % w/w to about 5% w/w, or alternatively from about 0.00001 % w/w to about 3% w/w, or alternatively from about 0.0001 % w/w to about 3% w/w, or alternatively from about 0.001 % w/w to about 3% w/w, or alternatively from about 0.01 % w/w to about 3% w/w, or alternatively from about 0.1 % w/w to about 3% w/w, wherein the total of all components of the formulation is to 100%.

[0064] The formulation can optionally comprise a viscosity-inducing agent that may be the same as or different from the mucoadhesive. As used herein, the term "viscosity inducing agent" intends a polymer or other agent that may or may not be a mucoadhesive, and is present in an amount of from about 0.01 % w/w to about 20% w/w, or alternatively from about 0.1 % w/w to about 20%, or alternatively from about 1% w/w to about 20% w/w, or alternatively from about 5% to about 20% w/w, or alternatively from about 10% w/w to about 20% w/w, from about 0.01 % w/w to about 15% w/w, or alternatively from about 0.1 % w/w to about 15%, or alternatively from about 1% w/w to about 15% w/w, or alternatively from about 5% to about 15% w/w, or alternatively from about 10% w/w to about 15% w/w, or alternatively from about 0.01 % w/w to about 10% w/w, or alternatively from about 0.1 % w/w to about 10%, or alternatively from about 1% w/w to about 10% w/w, or alternatively from about 5% to about 10% w/w, or alternatively less than 15% w/w, or alternatively less than 10% w/w, or alternatively less than 5% w/w, or alternatively less than 3%, to a total of 100% for the formulation. Non-limiting examples of such include one or more of agar, bentonite, glycerin, providone, kaolin, tragacanth, sodium alginate and cross-linked polyacrylic acids.

[0065] In a yet further aspect, the formulation further comprises, or consists essentially of, or yet further consists of, one or more of a therapeutically or a prophylactically active drug. As is apparent to the skilled artisan, the selection of the therapeutically and/or prophylactically active drug will depend on the ultimate use of the formulation and its mode of administration. In one aspect, one or more of the therapeutically active drug, the prophylactically active drug, the medicinal supplement or the nutritional supplement is

encapsulated within a nanoparticle, that optionally is conjugated or joined to a targeting moiety, as described above.

[0066] Applicants previously described in International Application No. PCT No. PCT/US2012/028138 (incorporated herein by reference), the encapsulation of therapeutically active agents for transport across membranes and these nanoparticle compositions can be used, in one aspect, in the disclosed formulations. The nanoparticles can optionally comprise a targeting agent, such as Vitamin B12 or other agents such as other B vitamins (e.g. folate, biotin), peptides (e.g. RGD), antibodies, and other targeting agent known in the art, for directed delivery of the encapsulated product. The nanoparticles will of course be biocompatible and biodegradable such that the encapsulated agent is delivered to the site of action upon administration.

[0067] For topical treatment of mucosal membranes, the formulations of this disclosure offer advantages over other dosage forms in that in one aspect a wide area of the mucosa can be readily covered with the solution, which is of benefit if the area to be treated is not a single, discrete region. Also, mucosa not readily accessible can be treated using aqueous solutions of pharmaceutically-active compounds and simple methods of application. However, formulations which are non-mucoadhesive and non-viscous are less than ideal for delivery of drugs to mucosal surfaces. Such solutions will be rapidly removed from the area being treated, for example, because the liquid flows from the site of application under the influence of gravity, and/or because the natural secretions of mucosal membranes carry the solution from the site of application.

[0068] For topical treatment of mucosal membranes, the formulations of this disclosure offer advantages over other dosage forms in that in one aspect a discrete area of the mucosa can be readily covered with the gel, which is of benefit if the area to be treated is a single, discrete region.

[0069] Applicants have discovered that neither high viscosity nor mucoadhesion alone confers ideal properties. A viscous but non-mucoadhesive liquid will not be held in place on the mucosal surface. Instead, a non-mucoadhesive solution will readily be lost from the point of application, for example, under the influence of gravity, and/or through natural movements of the membrane and surrounding structures, and/or the flow of natural secretions. In an aqueous liquid formulation which is mucoadhesive but has low viscosity, only a thin layer of

the liquid which is adjacent to the mucosa may be held in place, but the bulk of the liquid might rapidly flow from the site of application under the influence of gravity and/or be readily removed by the natural secretions of mucosal membranes. In a mucoadhesive, viscous liquid formulation, the liquid will adhere to the mucosa, while the high viscosity of the liquid will reduce the rate of removal of the bulk of the liquid from the site of application. In some cases a low viscosity mucoadhesive may provide effective treatment, especially when pharmaceutical agents are not required. A mucoadhesive agent may itself be a viscosity-inducer and thus serve two purposes.

[0070] For most liquids, viscosity remains constant over a wide range of shear rates. This phenomenon is known as Newtonian viscosity, and liquids which display this property are called Newtonian liquids. Liquids in which viscosity varies with shear rate are termed non-Newtonian. There are several known non-Newtonian profiles. One of these profiles is termed pseudoplastic, and liquids which fall into this category demonstrate a decrease in viscosity as shear rate increases. Formulations of the current disclosure are pseudoplastic, and demonstrate a decrease in viscosity at low shear rates. Pseudoplasticity benefits the application of the formulations of the current disclosure by virtue of the fact that application of shear (for example, swishing the liquid in the mouth) reduces the viscosity, so allowing the liquid to flow and coat the mucoscal surface more readily. Once the shear forces are discontinued, the viscosity of the liquid increases, as required (in combination with mucoadhesion) for prolonged attachment to the mucosal surface.

[0071] Formulations of the current disclosure are viscous, free-flowing liquids or mobile gels that are either Newtonian or pseudoplastic. The ability to flow freely or be spread freely is advantageous in order to readily coat either a selected region or a wide area of the affected mucosal membrane, and to coat mucosal membranes not readily accessible to simple application. The solutions of the current invention will have viscosities at zero shear in the range 100- 20,000 cP.

[0072] As noted above, the supplement can further comprise, or alternatively consisting essentially of, or yet further consist of, various agents in an amount to treat or prevent a mucocutaneous disorder. Non-limiting examples of a mucocutaneous disorder include mucositis, Behcet's disease, apthous ulcer, bullous pemphigoid, chemical cystitis, radiation cystitis, erythema multiforme, esophagitisis, interstitial cystitis, oral Lichen planus, pemphigus, radiation proctitis, or ulcerative colitis.

[0073] The stable, viscous, mucoadhesive liquid formulations are applied to mucosal membranes for the delivery of the agents. The formulations can be topically applied, e.g., to the following mucosal surfaces; the oral cavity, the nasal cavity, the gastrointestinal and respiratory tracts, the vagina, and/or the bladder. The formulations may also be applied to other mucous membranes for the prevention and treatment of disorders and diseases or for nutritional supplementation. Many methods known in the art for the delivery of liquids to body compartments may be used.

[0074] For administration to the oral cavity, the liquid formulations can be taken by mouth and distributed throughout the oral cavity by a swishing action, or by the patient adopting a slow circulating movement of the head. Excess solution can either be swallowed or expelled. For treatment of disorders and diseases of the oral cavity, the stable, mucoadhesive gel formulations may be taken by mouth and distributed throughout the oral cavity by the action of the tongue and/or use of a swab or similar device. Excess gel can either be swallowed or expelled.

[0075] For treatment of disorders and diseases of the esophagus, the stable mucoadhesive liquid and gel formulations can be swallowed with minimal contact of the oral cavity, or administered by gavage, or by spraying the liquid into the throat.

[0076] For treatment of disorders and diseases of the nasal cavity, the stable mucoadhesive liquid and gel formulations can be delivered as droplets or by spraying the liquid into the nose.

[0077] For treatment of disorders and diseases of the bladder, the stable, mucoadhesive liquid or gel formulations of the current disclosure can be delivered by intravesical administration.

[0078] For treatment of disorders and diseases of the rectum and lower gastrointestinal tract, the stable mucoadhesive liquid or gel formulations can be administered by catheter or enema.

[0079] Other methods to apply the stable, viscous, mucoadhesive liquid formulations and stable mucoadhesive gel formulations of the current disclosure to mucosal tissues are known to those skilled in the art.

[0080] The liquid or other formulations are ideally suited to treat diseases and disorders which affect a wide area of the mucosal surface, but they also provide the opportunity to treat discrete, localized lesions, especially in the oral cavity. The mucous membranes which may be treated by the formulations described herein include, but are not limited to, those in the oral cavity, the nasal cavity, the gastrointestinal and respiratory tracts, the vagina, and the bladder. Inflammatory, erosive, and/or ulcerative diseases which can be treated by topical application of the formulations described herein include, but are not limited to aphthous ulcers, Behçet syndrome, bullous pemphigoid, chemical or radiation-induced cystitis, erythema multiforme, esophagitis, interstitial cystitis, mucositis, oral lichen planus, pemphigus, and radiation proctitis. In conditions such as aphthous ulcers, chemical or radiation-induced cystitis, mucositis, and radiation proctitis, when the onset of the inflammatory, erosive, and/or ulcerative condition may be forecast (for example, by prodromal sensations in the case of aphthous ulcers, and by initiation of chemotherapy and/or radiation therapy in the treatment of cancer), the formulations of this invention might be applied prior to the formation of lesions, or at the commencement of therapy to prevent or delay the onset of inflammatory, erosive, and/or ulcerative lesions.

[0081] There is currently no complete explanation of why the viscous, mucoadhesive formulations should provide such benefit to patients. The following are considered viable possibilities, but this disclosure should not be considered as limited to any one of these possibilities.

[0082] A viscous, mucoadhesive formulation provides a layer on the surface of the mucosa for an extended period, and this may have a beneficial effect, for example, a moisturizing or barrier effect, to limit the damage to the mucosal surface caused by disease, or injury from ionizing radiation and/or chemotherapeutic agents. Thus, it is envisioned that any aqueous solution which is formulated with non-toxic and non-irritating excipients and providing a solution which is both viscous and mucoadhesive might be expected to provide benefit to patients suffering a disease or disorder of the mucosa. The medical food/nutritional supplement component of the current disclosure provides additional benefit, for example it might provide additional nutrients to patients that have a deficiency in such nutrients which could be a contributor to or consequence of the disease, or could be a consequence (side-effect) of the method of disease treatment.

[0083] It is known that polyanionic carbohydrate polymers and oligomers can have a beneficial effect in the treatment of mucosal disorders. For example, pentosan polysulfate and hyaluronic acid are known to provide benefit to patients with interstital cystitis (19). It is quite possible that other polyanionic and polycationic compounds, whether carbohydrate, of natural origin or synthetic, may also provide benefit in the prevention and treatment of mucosal disorders. Linear and partially cross-linked polyanionic polymers are included in the formulations described in the examples.

[0084] In additional to the medical food, the other components of the formulation may also individually or in combination also contribute to the medically beneficial effect of the mucoadhesive liquid or gel. Specific components used in the formulations described in the examples include benzyl alcohol, citric acid, glycerin, polysorbate 60, and saccharin. These alone or in combination with each other and/or the medical foods and/or the other excipients of the formulation may have a medically beneficial effect. Other preservatives, humectants, emulsifying agents, antioxidants, antimicrobial agents, solubilizing agents, and other excipients known in the art in the formulation of liquid pharmaceutical, medical device and medical food products, alone or in combination, may also provide for, or enhance, the beneficial properties on mucosal surfaces, when formulated to provide a viscous, mucoadhesive liquid or gel.

[0085] Viscous, mucoadhesive formulations containing medical foods for the prevention and treatment of mucosal diseases and disorders or other diseases may additionally be formulated with one or more compounds known to be pharmaceutically active. Addition of further pharmaceutically active compounds could provide greater benefit to patients in the prevention and treatment of mucosal or other disorders. Examples of pharmaceutically active compounds which could be incorporated in the viscous, mucoadhesive formulations of this disclosure are provided later in this section.

[0086] Viscous, mucoadhesive formulations containing nanoparticles or nutritional supplements for the prevention and treatment of mucosal diseases and disorders or other diseases may additionally be formulated with one or more compounds known to be pharmaceutically active. Addition of further pharmaceutically active compounds could provide greater benefit to patients in the prevention and treatment of mucosal or other disorders. Examples of pharmaceutically active compounds which could be incorporated in the viscous, mucoadhesive formulations are described herein.

[0087] Aqueous solutions of medical food and/or nutritional supplements are well known in the art as convenient formulations for oral delivery of the medical food/ nutritional supplement. When such formulations are swallowed, the medical food/nutritional supplement is presented to the stomach and gastrointestinal tract in a form which is amenable to rapid absorption. In general, aqueous solutions used to deliver medical foods or nutritional supplements tend to be non-viscous and non-mucoadhesive. The viscous mucoadhesive liquid formulations cause more of the medical food to be in contact with the mucosa, and for a longer duration, than is the case for non-viscous and non-mucoadhesive liquids. This provides greater potential for absorption of the medical food/nutritional supplement through the mucosa, providing faster delivery to the bloodstream and faster onset of the beneficial effect. If the medical food/nutritional supplement is providing its benefit through mucosal contact, then the ability of the viscous, mucoadhesive liquid to hold more of the medical food/nutritional supplement in place on the mucosa provides for enhanced benefit compared with non-viscous and non-mucoadhesive formulations.

[0088] For topical treatment of mucosal membranes, aqueous solutions of the medical food/nutritional supplement offer the advantage over other dosage forms in that a wide area of the mucosa can be readily covered with the solution, which is of benefit if the area to be treated is not a single, discrete region. Also, mucosa not readily accessible can be treated using viscous, mucoadhesive aqueous solutions of medical foods and/or nutritional supplements and simple methods of application. However, formulations which are non-mucoadhesive and non-viscous are less than ideal for delivery of medical foods and/or nutritional supplements to mucosal surfaces. Such solutions will be rapidly removed from the area being treated, for example, because the liquid flows from the site of application under the influence of gravity, and/or because the natural secretions of mucosal membranes carry the solution from the site of application.

[0089] One aspect of the current disclosure involves a finding that neither high viscosity nor mucoadhesion alone confers ideal properties to the formulation containing either a medical food, nutritional supplement, nanoparticles, or targeted conjugates, or some combination thereof. A viscous but non-mucoadhesive liquid or gel will not be held in place on the mucosal surface. Instead, a non-mucoadhesive solution will readily be lost from the point of application, for example, under the influence of gravity, and/or through natural movements of the membrane and surrounding structures, and/or the flow of natural

secretions. In an aqueous liquid formulation which is mucoadhesive but has low viscosity, only a thin layer of the liquid which is adjacent to the mucosa may be held in place, but the bulk of the liquid might rapidly flow from the site of application under the influence of gravity and/or be readily removed by the natural secretions of mucosal membranes. In a mucoadhesive, viscous liquid formulation, the liquid will adhere to the mucosa, while the high viscosity of the liquid will reduce the rate of removal of the bulk of the liquid from the site of application. In some cases, a low viscosity mucoadhesive may provide effective treatment, especially when pharmaceutical agents are not required. A mucoadhesive agent may itself be a viscosity-inducer and thus serve two purposes. The term "viscosity-inducing" is meant to mean enhancement of the aqueous mucoadhesive layer that adheres to mucosal areas.

[0090] Mucoadhesive formulations are well known in the art. However, known formulations intended for extended delivery of a drug or medical food to (or close to) the site of application of a mucoadhesive formulation are either liquids or gels. Examples of mucoadhesive gels include gels, pastes, ointments, and creams.

[0091] For most liquids, viscosity remains constant over a wide range of shear rates. This phenomenon is known as Newtonian viscosity, and liquids which display this property are called Newtonian liquids. Liquids in which viscosity varies with shear rate are termed non-Newtonian. There are several known non-Newtonian profiles. One of these profiles is termed pseudoplastic, and liquids which fall into this category demonstrate a decrease in viscosity as shear rate increases. Preferred formulations of the current disclosure are pseudoplastic, and demonstrate a decrease in viscosity at low shear rates. Pseudoplasticity benefits the application of the formulations of the current invention by virtue of the fact that application of shear (for example, swishing the liquid in the mouth) reduces the viscosity, so allowing the liquid to flow and coat the mucosal surface more readily. Once the shear forces are discontinued, the viscosity of the liquid increases, as required (in combination with mucoadhesion) for prolonged attachment to the mucosal surface.

[0092] Formulations of the current invention are either gels or viscous, free-flowing liquids (i.e., not gels) that are either Newtonian or pseudoplastic. The ability to flow freely is desired in order to readily coat either a selected region or a wide area of the affected mucosal membrane, and to coat mucosal membranes not readily accessible to simple application. The

solutions of the current disclosure will have viscosities at zero shear in the range 100- 20,000 cps.

[0093] Other methods to apply the stable, viscous, mucoadhesive liquid formulations of the current disclosure to mucosal tissues are known to those skilled in the art.

[0094] There are a very large number of nanoparticle systems which are suitable for delivery to significant body compartment of molecules important for the prevention and treatment of disease. Examples include polymer systems, metals, lipids, insoluble salts, etc. Various nanoparticulate drug delivery systems have been referenced in multiple reviews (examples; 20-25). All cited nanoparticle systems suitable for delivery of compounds for medical or nutritional benefit are incorporated by reference in this invention. Other nanoparticle systems that potentially can be formulated with the viscous, mucoadhesive liquids or gels will be known to those skilled in the art. Dependent upon nanoparticle stability and drug-loading stability in the viscous, mucoadhesive formulations of this disclosure, the nanoparticles can be formulated in the viscous, mucoadhesive formulations at the time of manufacture, or can be prepared separately and the nanoparticles mixed with the viscous, mucoadhesive formulation immediately prior to administration to a human or animal subject.

[0095] An embodiment of this disclosure is a nanoparticle system in which is encapsulated one or more medical foods and/or nutritional supplements wherein the nanoparticles are coated with a targeting group.

[0096] An embodiment of this disclosure is a nanoparticle system in which is encapsulated one or more medical foods and/or nutritional supplements wherein the nanoparticles are coated with a targeting group, such as folic acid, biotin, or B vitamins, such as vitamin B12. An embodiment of this disclosure is a nanoparticle system in a viscous, mucoadhesive liquid or gel wherein the nanoparticles are coated with a targeting group, such as folic acid, biotin or B vitamin, such as vitamin B12.

[0097] Another embodiment of this disclosure is a nanoparticle system containing a pharmaceutically-active agent in a viscous, mucoadhesive liquid or gel containing one or more medical foods and/or nutritional supplements wherein the nanoparticles are coated with a targeting group, such as folic acid, biotin or B vitamin, such as vitamin B12.

[0098] A further embodiment of this disclosure is a nanoparticle system in a viscous, mucoadhesive formulation wherein the nanoparticles are coated with vitamin B12 as a targeting group. The coating can be provided by physical coating with vitamin B12 or a vitamin B12 derivative, or by covalent linkage of the vitamin B12 to the surface the nanoparticle or to one of the components of the nanoparticle. Nanoparticles with vitamin B12 appearing on the surface are known in the art (26-30), and such nanoparticles are incorporated by reference.

[0099] A large number of targeted-conjugates are known in the art, and have been referenced in multiple reviews (examples; 31-34). All cited targeted-conjugate systems suitable for delivery of compounds for medical or nutritional benefit are incorporated by reference in this invention. Other targeted-conjugate systems that potentially can be formulated with the viscous, mucoadhesive liquids will be known to those skilled in the art. Dependent upon targeted-conjugate stability in the viscous, mucoadhesive liquids of this invention, the targeted-conjugates can be formulated in the viscous, mucoadhesive liquid at the time of manufacture, or can be prepared separately and the targeted-conjugates mixed with the viscous, mucoadhesive liquid immediately prior to administration to a human or animal subject.

[0100] An embodiment of this disclosure is a targeted-conjugate system wherein the moiety being targeted is a nutritional supplement or medical food, and the targeting group and medical food/nutritional supplement are covalently linked directly or via a linker.

[0101] Another aspect of this disclosure is a targeted-conjugate system wherein the moiety being targeted is a nutritional supplement or medical food and the targeting group is a B vitamin, such as folic acid, biotin or vitamin B12, and the targeting group and medical food/nutritional supplement are covalently linked directly or via a linker.

[0102] A yet further aspect of this disclosure is a targeted-conjugate system in a viscous, mucoadhesive liquid or gel wherein the targeting group is a B vitamin, such as folic acid, biotin or vitamin B12.

[0103] A preferred embodiment of this disclosure is a targeted-conjugate system in a viscous, mucoadhesive liquid or gel wherein the targeted-conjugates have vitamin B12 as the targeting group. Targeted-conjugates with vitamin B12 as the targeting group are known in

the art (35-41), and such targeted-conjugates are incorporated by reference. Other vitamin B12 targeted conjugates will be known or self-evident to those skilled in the art.

[0104] Three aspects of this invention can optionally involve pharmaceutically-active compounds. For nanoparticles, pharmaceutically-active compounds could be formulated in or on the nanoparticle for delivery of the pharmaceutically-active compound to the disease site. For targeted-conjugates, the pharmaceutically-active compound can be conjugated to the targeting group. And for viscous mucoadhesive liquid formulations with or without nanoparticles or targeted-conjugates, but containing a medical food, nutritional supplement, or a combination of medical foods and nutritional supplements, the formulation may optionally contain one or more pharmaceutically-active compounds for added medical benefit formulated in the viscous mucoadhesive liquid or gel.

[0105] Pharmaceutically active compounds which may be formulated in nanoparticles, as targeted conjugates or within the viscous, mucoadhesive liquid medical food/nutritional supplement formulations of the current disclosure can include, either alone or in combination, one or more of the following classes of drugs: anti-allergy compounds, anti-inflammatory analgesic agents, steroidal and non-steroidal anti-inflammatory agents, anabolic steroids, analgesics, antihistamines, local anesthetics, bactericides and disinfectants, vasoconstrictors, hemostatics, chemotherapeutic agents, antibiotics, antidiabetic agents, keratolytics, cauterizing agents, and antiviral drugs. Other classes of pharmaceutically active agents may also be formulated with the viscous, mucoadhesive liquid formulations (within nanoparticles, as targeted-conjugates or directly within the liquid formulation) of the current disclosure.

[0106] Examples of anti-inflammatory analgesic agents include acetaminophen, methyl salicylate, monoglycol salicylate, aspirin, mefenamic acid, flufenamic acid, indomethacin, diclofenac, alclofenac, diclofenac sodium, ibuprofen, ketoprofen, naproxen, pranoprofen, fenoprofen, sulindac, fenclofenac, clidanac, flurbiprofen, fentiazac, bufexarnac, piroxicam, phenylbutazone, oxyphenbutazone, clofezone, pentazocine, mepirizole, tiaramide hydrochloride, etc.

[0107] Examples of steroidal anti-inflammatory agents include hydrocortisone, predonisolone, dexamethasone, triamcinolone acetonide, fluocinolone acetonide, hydrocortisone acetate, predonisolone acetate, methylpredonisolone, dexamethasone acetate,

betamethasone, betamethasone valerate, flumetasone, fluorometholone, beclomethasone diproprionate, etc.

[0108] Examples of anabolic steroids include testosterone and oxandrolone.

[0109] Examples of antihistamines include diphenhydramine hydrochloride, diphenhydramine salicylate, diphenhydramine, chlorpheniramine hydrochloride, chlorpheniramine maleate isothipendyl hydrochloride, tripelennamine hydrochloride, promethazine hydrochloride, methdilazine hydrochloride, etc.

[0110] Examples of local anesthetics include dibucaine hydrochloride, dibucaine, lidocaine hydrochloride, lidocaine, benzocaine, p-buthylaminobenzoic acid 2-(die-ethylamino) ethyl ester hydrochloride, procaine hydrochloride, tetracaine, tetracaine hydrochloride, chloroprocaine hydrochloride, oxyprocaine hydrochloride, mepivacaine, cocaine hydrochloride, piperocaine hydrochloride, dyclonine, dyclonine hydrochloride, etc.

[0111] Examples of bactericides and disinfectants include thimerosal, phenol, thymol, benzalkonium chloride, benzethonium chloride, chlorhexidine, povidone iode, cetylpyridinium chloride, eugenol, trimethylammonium bromide, etc.

[0112] Examples of vasoconstrictors include naphazoline nitrate, tetrahydrozoline hydrochloride, oxymetazoline hydrochloride, phenylephrine hydrochloride, tramazoline hydrochloride, etc.

[0113] Examples of hemostatics include thrombin, phytonadione, protamine sulfate, aminocaproic acid, tranexamic acid, carbazochrome, carbaxochrome sodium sulfanate, rutin, hesperidin, etc.

[0114] Examples of chemotherapeutic drugs include sulfamine, sulfathiazole, sulfadiazine, homosulfamine, sulfisoxazole, sulfisomidine, sulfamethizole, nitrofurazone, taxanes, platinum compounds, topoisomerase I inhibitors, and anthracycline.

[0115] Examples of antibiotics include penicillin, meticillin, oxacillin, cefalotin, cefalordin, erythromcycin, lincomycin, tetracycline, chlortetracycline, oxytetracycline, metacycline, chloramphenicol, kanamycin, streptomycin, gentamicin, bacitracin, cycloserine, and clindamycin.

[0116] Examples of antidiabetics include insulin and insulin derivatives, sulfonylurea (e.g. glyburide, glimepiride, glipizide), Biguanides (metformin, phenformin, buformin), alpha-

glucosidase inhibitor (e.g. acarbose, miglitol, voglibose), thiazolidinediones (pioglitazone, rosiglitazone), meglitinides (repaglinide, nateglinide), incretin mimetics (exenatide, liraglutide), dipeptidyl peptidase-4 inhibitors, and DPP-4 inhibitors.

[0117] Examples of keratolytics include salicylic acid, podophyllum resin, podolifox, and cantharidin. Examples of cauterizing agents include the chloroacetic acids and silver nitrate.

[0118] Examples of antiviral drugs include protease inhibitors, thymadine kinase inhibitors, sugar or glycoprotein synthesis inhibitors, structural protein synthesis inhibitors, attachment and adsorption inhibitors, and nucleoside analogues such as acyclovir, penciclovir, valacyclovir, and ganciclovir.

[0119] Examples of anti-allergy compounds include alopatadine, astemizole, cromolyn, fenpiprane, repirinast, tranilast, traxanox, etc.

[0120] The amount of pharmaceutically active compound(s) to be used depends on the desired treatment strength, although preferably, the pharmaceutical component comprises 0.001 to 30% by weight of the formulation, or alternatively between 0.005 and 20% by weight.

[0121] In addition to the properties of mucoadhesion and viscosity as described above, it is important that the liquid or gel be stable, such that it can be stored at ambient temperatures for many months or years, even when subjected to brief periods of elevated or depressed temperatures, without physical or chemical degradation of the formulation. It is usually desirable to formulate the product without use of any organic solvents, the presence of which might irritate the mucosal lesions being treated, although liquid and gel formulations containing pharmaceutically-acceptable organic solvents are within the scope of this disclosure provided that the incorporation of such solvents does no harm to the mucosa, and possibly provides benefit; for example, as disinfectants, or to aid the solvation of the mucous membrane to provide more rapid mucoadhesion, or for concentration of the excipients (through evaporation of the solvent following application to the mucosa) to enhance mucoadhesion and/or viscosity following application. Furthermore, it is desirable to formulate the viscous, mucoadhesive solution using only excipients which are accepted by all major pharmaceutical regulating authorities as safe.

[0122] It is within the scope of this disclosure that when components are not stable for many months that they be provided as two or more stable formulations in kit form with

instructions, and that the formulations be combined immediately prior to administration to a patient

[0123] Viscosity enhancement can be provided by one or more of the above mentioned mucoadhesive polymers alone or in combination with agar, bentonite, glycerin, povidone, kaolin, and/or tragacanth and sodium alginate. In one aspect, the combination is Carbopol and glycerin.

[0124] The pH of the solution is adjusted to the final desired pH with any pharmaceutically accepted acid or base, e.g., sodium or potassium hydroxide, phosphoric acid, or citric acid. A final pH of 6.5 to 9.5 is preferred.

[0125] To prevent microbial growth in the formulation during storage, it is desirable to include a preservative. Preservatives known in the art include benzyl alcohol, benzoate salts, phenoxyethanol, methylparaben, and propylparaben. Phenoxyethanol and benzyl alcohol are the most preferred preservatives.

[0126] A humectant is desirable to provide a pleasant mouth-feel in oral applications. Humectants known in the art include cholesterol, fatty acids, glycerin, lauric Acid, magnesium stearate, pentaerythritol, and propylene glycol. Glycerin is preferred.

[0127] An emulsifying agent might be necessary, for example to ensure complete dissolution of all excipients, especially hydrophobic components such as benzyl alcohol. Many emulsifiers are known in the art. In one aspect the emulsifier is polysorbate 60.

[0128] For oral applications, it may be desirable to add a pharmaceutically acceptable flavoring agent, coloring agent and/or sweetener. Compounds such as artificial and natural sweetners, e.g., saccharin, glycerin, simple syrup, and sorbitol are useful among those as sweeteners.

[0129] It may be desirable to include other ingredients; for example a pharmaceutically acceptable carrier, an organic solvent, a buffering agent, an antioxidant, a free radical scavenger, an antimicrobial agent, and/or a coloring agent. The exact formulation of the above ingredients, and the method of manufacture, will be apparent to those skilled in the art. A number of texts provide assistance in the design and manufacture of pharmaceutical formulations, including Remington's Pharmaceutical Sciences, Mack Publishing Company

Co., Easton, Pa., and Pharmaceutical dosage forms and drug delivery, Ansel et al, 1995, Williams and Wilkins, Malvern, Pa.

[0130] In one aspect, the gel or liquid formation comprises one or more mucoadhesive selected from the group of a linear or cross-linked polymer of the group, e.g., a polyacrylic acid, a carboxymethylcellulose, a hydroxyalkyl cellulose, a dextran sulfate, a dermatan sulfate, a water-soluble vinyl polymer, chitosan, in an amount from about 0.1% (w/w) to about 10% (w/w), or alternatively from about 0.5% (w/w) to about 5%, or alternatively from about 0.5% (w/w) to about 3 % (w/w) or alternatively about 1% (w/w). In one aspect, the mucoadhesive is a Carbopol® , e.g., Carbopol 971®P. The formulation can optionally comprise a viscosity-inducing agent or enhancer, e.g., one or more of agar, bentonite, glycerin, providone, kaoline, or tragacanth, in an amount from about 1% (w/w) to about 10% (w/w), or alternatively from about 2% (w/w) to about 7% (w/w), or alternatively from about 2% (w/w) to about 6% (w/w), or alternatively from about 2.5 % (w/w) to about 5% (w/w). In one aspect, the viscosity-inducing agent is glycerin. The formulations contain a nutritional supplement, e.g., ferrous sulfate, from about 1.0% (w/w) to about 5% (w/w), or alternatively from about 2.0% (w/w) to about 3% (w/w), or alternatively about 2.5% (w/w). In one aspect, the nutritional supplement is in the formulation in a dispersion, or alternatively, within a nanoparticle, optionally coated with a targeting moiety. When formulated as a liquid, the formulation can be pseudoplastic, and having a viscosity as described above, and incorporated herein by reference. In one aspect, the above noted formulations can further comprise one or more of a sweetener, a coloring agent, or a buffer. They can further comprise one or more of a pharmaceutically acceptable carrier, an organic solvent, an antioxidant, a free radical scavenger, a preservative, or an antimicrobial agent.

[0131] The final pH of a liquid formulation is between about 3 to 9, or alternatively from about 5 to 9, or alternatively from about 6.5 and about 8.5.

Therapeutic and Nutritional Methods

[0132] This disclosure provides methods for delivering one or more medical food, nutritional supplement or therapeutic agent contained within the formulation by administering to a subject, such as a human patient in need of such agent, an effective amount of the formulation as described herein. Modes of administration are described above and known to those of skill in the art, and include without limitation, oral or topical.

[0133] This disclosure also provides methods for treating a mucocutaneous surface or a mucocutaneous disorder in a subject in need thereof, by administering to a subject, such as a human patient, an effective amount of the formulation as described herein. Modes of administration are described above and known to those of skill in the art, and include without limitation, orally or topically. In one aspect, the administration to the subject is by gargling or swishing the supplement in the oral cavity by the subject.

[0134] As used herein, the term "mucocutaneous" area intends a mucous membrane that provides a protective layer on the surface of several body cavities, including but not limited to the oral cavity, the nasal cavity, the gastrointestinal (rectal, colon or intestinal) and respiratory tracts, the vagina, the bladder and the urinary tract.

[0135] A mucocutaneous disorder is a condition that causes discomfort to a patient or subject. Non-limiting examples of such include mucositis, Behcet's disease, apthous ulcer, bullous pemphigoid, chemical cystitis, radiation cystitis, erythema multiforme, esophagitis, interstitial cystitis, oral Lichen planus, pemphigus, radiation proctitis, or ulcerative colitis.

[0136] Aphthous ulcers (also known as aphthous stomatitis and canker stores) are benign open sores in the mouth, which appear as a painful white or yellow sore (ulcer) surrounded by a bright red area. Aphthous ulcers can be categorized into three groups: minor aphthous ulcers, the most common type, which recur in crops of 1 to 5 lesions, are less than 1 cm in diameter each, and usually affect the lips, buccal mucosa, mucobuccal and mucolabial sulci, and tongue; major aphthous ulcers, which are greater than 2 cm in diameter, begin as solitary nodules, and subsequently destroy deeper tissue, resulting in scarring that affects the movable oral mucosa and posterior mucosal surfaces; and herpetiform ulcers, which are recurrent, multiple (10 to 100), shallow, pinpoint lesions 1 to 2 mm in diameter that may affect any part of the mucosa. The cause for any of the three types is not known, although autoimmune mechanisms are suspected.

[0137] Aphthous ulcers are occasionally associated with macrocytic anemias or gluten-sensitive enteropathy and may become more frequent and severe in association with human immunodeficiency virus (HIV) infection (11).

[0138] Behcet's disease is a chronic multisystem disease characterized by oral and genital aphthae, arthritis, cutaneous lesions, and ocular, gastrointestinal, and neurologic manifestations. It was first described by the Turkish dermatologist Hulusi Behcet in 1937 as

"recurrent oral aphthous ulcers, genital ulcers, and 'hypopyon-uveitis.'" The diagnosis of Behcet's disease is based on clinical criteria as established by O'Duffy and Goldstein and the International Study Group. Complex aphthosis is the presence of almost constant, multiple oral and genital aphthae in the absence of systemic manifestations. These patients must be distinguished from those with Behcet's disease.

[0139] Bullous pemphigoid (BP) is an autoimmune, subepidermal blistering disease. The antigenic targets are components of the hemidesmosome; the 230-kD bullous pemphigoid antigen 1 and the 180-kD bullous pemphigoid antigen 2. It commonly affects patients in their seventh decade. About 40% of patients will experience oral involvement during the course of their disease.

[0140] The mainstay of treatment for BP is systemic corticosteroids. Bullous pemphigoid is usually exquisitely sensitive to these drugs, but significant side-effects in a predominantly elderly patient population limits their long-term use at therapeutic doses. Steroid-sparing agents, such as dapsone, methotrexate, and azathioprine, have been used successfully. In addition, tetracycline and niacinamide have been shown to be effective, and this combination is frequently tried first to avoid toxicity from other drugs (14).

[0141] The term 'cystitis' covers a range of disorders commonly known as "painful bladder" disease in which diagnosed patients suffer bladder and/or pelvic pain and irritative voiding symptoms (urgency, frequency, nocturia, dysuria). There are a variety of known causes, which include the damaging side-effects of radiation therapy to the lower abdomen, and cytotoxic agents and/or their metabolites as they pass through the bladder following renal clearance.

[0142] Erythema multiforme often affects the oral cavity and is frequently recurrent. The classic cutaneous findings are targetoid lesions symmetrically distributed over the trunk and extremities. Studies show that as many as 70% of patients develop oral lesions, which are extremely painful and often debilitating. In more than 60% of patients, the attacks followed an episode of herpes simplex virus (HSV) infection. Acyclovir or one of the newer antiviral agents can be used to suppress recurrent HSV outbreaks and to prevent recurrent erythema multiforme. The current recommendations for daily suppression of HSV are acyclovir (400 mg twice daily), famciclovir (250 mg twice daily), or alacyclovir (500 mg daily). Suppressive

doses are to be used for patients who experience more than six episodes a year of HSV or HSV-induced erythema multiforme.

[0143] Gastroesophageal reflux disease (GERD) is the most common cause of esophagitis. Esophagitis also is a side effect of radiation. Esophagitis is also caused by adverse reaction to certain medications.

[0144] Interstitial cystitis (IC) has only recently been recognized as a major health problem. It encompasses a major portion of the "painful bladder" disease complex, which includes a large group of urologic patients with bladder and/or pelvic pain, irritative voiding symptoms (urgency, frequency, nocturia, dysuria), and negative urine cultures. Painful bladder diseases with a well-known cause include radiation cystitis, cyclophosphamide cystitis, cystitis caused by microorganisms that are not detected by routine culture methodology, and systemic diseases affecting the bladder.

[0145] Oral mucositis is a significant problem in patients receiving chemotherapy or radiation therapy. Estimates of oral mucositis in cancer therapy range from 40% of those receiving standard chemotherapy to 76% of bone marrow transplant patients. Virtually all patients who receive radiation therapy to the head and neck area develop oral complications. Mucositis is not only painful, but it also can limit adequate nutritional intake and decrease the willingness of patients to continue treatment. More severe mucositis with extensive ulceration may require costly hospitalizations with parenteral nutrition and narcotics. Mucositis diminishes the quality of life and may result in serious clinical complications. A healthy oral mucosa serves to clear microorganisms and provides a chemical barrier that limits penetration of many compounds into the epithelium. A mucosal surface that is damaged increases the risk of a secondary infection and may even prove to be a nidus for systemic infection. Mucositis may result in the need to reduce dosage in subsequent chemotherapy cycles or to delay radiation therapy, which may ultimately affect patient response to therapy.

[0146] Normally, cells of the mouth undergo rapid renewal over a 7- to 14-day cycle. Both chemotherapy and radiation therapy interfere with cellular mitosis and reduce the ability of the oral mucosa to regenerate. Cancer chemotherapeutic drugs that produce direct stomatotoxicity include the alkylating agents, antimetabolites, natural products, and other synthetic agents such as hydroxyurea and procarbazine hydrochloride. Typical sequelae of these cytotoxic agents include epithelial hyperplasia, collagen and glandular degeneration,

and epithelial dysplasia. Mucositis is an inevitable side effect of radiation. The severity of the mucositis is dependent on the type of ionizing radiation, the volume of irradiated tissue, the dose per day, and the cumulative dose. As the mucositis becomes more severe, pseudomembranes and ulcerations develop. Poor nutritional status further interferes with mucosal regeneration by decreasing cellular migration and renewal.

[0147] Direct stomatotoxicity is usually seen 5 to 7 days after the administration of chemotherapy or radiation therapy. In the nonmyelosuppressed patient, oral lesions heal within 2 to 3 weeks. The nonkeratinized mucosa is most affected. The most common sites include the labial, buccal, and soft palate mucosa, as well as the floor of the mouth and the ventral surface of the tongue. Clinically, mucositis presents with multiple complex symptoms. It begins with asymptomatic redness and erythema and progresses through solitary white elevated desquamative patches that are slightly painful to contact pressure. Following this, large, acutely painful contiguous pseudomembranous lesions will develop with associated dysphagia and decreased oral intake. Histopathologically, edema of the rete pegs is noted, along with vascular changes that demonstrate a thickening of the tunica intima with concomitant reduction in the size of the lumen and destruction of the elastic and muscle fibers of the vessel walls. The loss of the epithelial cells to the basement membrane exposes the underlying connective tissue stroma with its associated innervation, which, as the mucosal lesions enlarge, contributes to increasing pain. Oral infections, which may be due to bacteria, viruses, or fungal organisms, can further exacerbate the mucositis as well as lead to systemic infections. If the patient develops both severe mucositis and thrombocytopenia, oral bleeding may occur that is very difficult to treat.

[0148] A mucositis grading system gives the physician the ability to assess the severity of the mucositis in terms of both the pain and the patient's ability to maintain adequate nutrition so that a treatment plan can be appropriately constructed. There are many different grading systems; most are based on two or more clinical parameters, including erythema, pain, and problems with eating. An example of a common grading system is that proposed by the National Cancer Institute, which uses a numbering scale of 0 to 4. Grade 0 means no mucositis; grade 1, the patient has painless ulcers, erythema, or mild soreness; grade 2, the patient has painful erythema, edema, or ulcers but can eat; grade 3, the patient has painful erythema, edema, or ulcers and cannot eat; and grade 4, the patient requires parenteral or enteral support.

[0149] Lichen planus (LP) is a common, idiopathic skin disorder affecting approximately 2% of the adult US population. Although its behavior on the skin is predictable and manageable using topical corticosteroids, oral lichen planus (OLP) has a more variable clinical course and is less responsive to topical corticosteroid therapy. There are multiple clinical presentations of OLP, and the disorders in some of these clinical forms can mimic many other types of oral lesions. Furthermore, some authors believe that certain clinical types of OLP may have a premalignant nature. Various drugs, topical and systemic, have been shown to induce lichenoid lesions through antigenic mechanisms.

[0150] There is even good evidence emerging that amalgam and dental plaque can act as antigens to induce OLP in some patients. The plaque form of OLP is seen more often in smokers. Women appear to be affected more often than men. Not all persons who develop skin lesions develop OLP at the same time and vice versa. Those patients who develop skin lesions only are usually free of their LP in approximately 18 months; however, patients with OLP may have their lesions for up to 20 years. Thus, management strategies for the patient with OLP are markedly different than for its skin surface counterpart.

[0151] The most common oral presentation of LP is the reticular form. These lesions appear as raised white, linear striations that often interlace in what is termed striae of Wickham. These striations are almost pathognomonic of the disorder. It should be noted that these linear lesions also accompany the erosive form of OLP and occur at the periphery of the eroded area. This is a significant diagnostic clue in the evaluation of the erosive type. The reticular form usually is observed on the buccal mucosa, often bilaterally. Several authors have noted that these lesions are adjacent to gold or silver amalgam restorations in many cases. The lesions are asymptomatic.

[0152] The bullous form of OLP is uncommon, perhaps because the oral cavity is a very active region. The functions of chewing, swallowing, and speaking probably do not allow the bulla to remain intact for very long. The size of these lesions is variable, from a few millimeters to several centimeters. The plaque type of OLP appears as a nondescript leukoplakia that needs to be biopsied if no other diagnosis can be made for the lesion. These lesions appear as multiple diffuse, raised white plaques commonly on the buccal mucosa and tongue. Silverman et al have determined that patients with this form of LP tend to be smokers. This may place them at risk for transformation to dysplasia or carcinomatous change.

[0153] The atrophic form of OLP can be seen concomitantly with the erosive or reticular forms. This is frequently the type of OLP seen on the gingiva of patients, commonly referred to as desquamative gingivitis. These lesions are symptomatic. The patient may complain of burning and pain while brushing. Because dental plaque has been implicated as a possible antigen, the patient will need to see a dentist for professional maintenance following initial corticosteroid treatment of the lesions.

[0154] Erosive LP is the most painful form of OLP. As stated previously, these erosions are seen frequently with the reticular form adjacent to the area. Atrophic or plaque forms may be seen less commonly. Erosive LP may mimic oral cancer, erythema multiforme, lupus erythematosus, and candidiasis. Many drugs can produce lesions that look like erosive LP clinically (18).

[0155] Pemphigus is a rare, autoimmune blistering disease. Of the various forms of pemphigus, pemphigus vulgaris and paraneoplastic pemphigus affect the oral mucosa with regularity. The antigenic targets in pemphigus are components of the desmosome. Binding of autoantibodies to these antigenic proteins, desmogleins and desmoplakins, leads to dissolution of intercellular adhesion with resultant blister formation. Activity of the disease correlates with titers of pemphigus antibody, which can be detected in the serum of patients with the disease by indirect immunofluorescence testing.

[0156] Pemphigus was often a fatal disease before the use of systemic corticosteroids. It has a chronic course, and control of the disease becomes more difficult with subsequent flares. The basis of treatment is immunosuppression to decrease antibody synthesis. Relapses may occur when immunosuppressive drugs are tapered. Paraneoplastic pemphigus remains a very difficult disease to treat and continues to have very high mortality rates.

[0157] Acute complications of pelvic radiation occur with distinct clinical courses and pathologic manifestations. The most frequent serious complication of pelvic radiation is small bowel damage, including thrombocytopenia, leukopenia, dysuria, and effects on the small bowel (diarrhea, abdominal cramping, and increased bowel frequency) and large bowel (acute proctitis, tenesmus, bloody and/or mucus discharge). Sigmoidoscopy during treatment normally reveals an inflamed, edematous, and friable rectal mucosa consistent with acute radiation proctitis. These symptoms are usually transient and resolve within a few weeks following the completion of radiation therapy. They appear to be a function of the dose rate

and fraction size rather than the total dose. The mechanism is primarily the depletion of actively dividing cells in what is otherwise a stable cell renewal system. In the small bowel, loss of the mucosal cells results in malabsorption of various substances including fat, carbohydrate, protein, and bile salts. The management of bowel-related complications usually involves the use of diphenoxylate and/or narcotics. The bowel mucosa usually recovers in 1 to 3 months following the completion of radiation (15).

[0158] Inflammatory bowel diseases (IBD), including ulcerative colitis and Crohn's disease, are chronic inflammatory diseases of the gastrointestinal tract. They are diagnosed by a set of clinical, endoscopic, and histologic characteristics, but no single finding is absolutely diagnostic for one disease or the other. Moreover, some patients have a clinical picture that falls between the two diseases and are said to have indeterminate colitis.

[0159] The inflammatory response in ulcerative colitis is largely confined to the mucosa and submucosa, but in Crohn's disease the inflammation extends through the intestinal wall from mucosa to serosa. Ulcerative colitis is confined to the colon, and colectomy is a curative procedure. Crohn's disease, in contrast, can involve any part of the gastrointestinal tract, although the distal small bowel and the colon are most commonly involved. Resection of the inflamed segment is not curative in Crohn's disease, and inflammation is likely to recur.

[0160] In ulcerative colitis, inflammation begins in the rectum, extends proximally a certain distance, and then abruptly stops, with a clear demarcation between involved and uninvolved mucosa. In mild disease, there are superficial erosions, whereas in more severe disease, ulcers may be large but superficial, penetrating the muscularis mucosa only in very severe disease. Inflammatory polyps or pseudopolyps may be present. Most of the pathologic findings in ulcerative colitis are limited to the mucosa and submucosa; the muscularis propria is affected only in fulminant disease. Active ulcerative colitis is marked by neutrophils in the mucosa and submucosa and clumps of neutrophils in crypt lumens (crypt abscesses). There is mucus depletion, mucosal edema, and vascular congestion with focal hemorrhage. In addition to signs of acute activity, there are also signs of chronicity, with lymphoid aggregates, plasma cells, mast cells, and eosinophils in the lamina propria.

[0161] The dominant symptom in ulcerative colitis is diarrhea, which is usually associated with blood in the stool. Bowel movements are frequent but small in volume as a result of irritability of the inflamed rectum. Urgency and fecal incontinence may limit the patient's

ability to function in society. Other symptoms include fever and pain, which may be in either lower quadrant or in the rectum. Systemic features--fever, malaise, and weight loss--are more common if all or most of the colon is involved and may have a greater effect than diarrhea on the patient's ability to function. Some patients, especially elderly persons, complain of constipation rather than diarrhea because rectal spasm prevents the passage of stool. The initial attack of ulcerative colitis may be fulminant with bloody diarrhea, but more commonly the disease begins indolently, with non-bloody diarrhea progressing to bloody diarrhea. Ulcerative colitis can present initially with any extent of anatomic involvement, from disease confined to the rectum to pancolitis. Most commonly, ulcerative colitis follows a chronic intermittent course with long periods of quiescence interspersed with acute attacks lasting weeks to months; however, a significant percentage of patients suffer a chronic continuous course (11).

[0162] The stable, viscous, mucoadhesive liquid formulations are applied to mucosal membranes for the delivery of the agents. The formulations can be topically applied, e.g., to the following mucosal surfaces; the oral cavity, the nasal cavity, the gastrointestinal and respiratory tracts, the vagina, and/or the bladder. The formulations may also be applied to other mucous membranes for the prevention and treatment of disorders and diseases or for nutritional supplementation. Many methods known in the art for the delivery of liquids to body compartments may be used.

[0163] For administration to the oral cavity, the liquid formulations can be taken by mouth and distributed throughout the oral cavity by a swishing action, or by the patient adopting a slow circulating movement of the head. Excess solution can either be swallowed or expelled. For treatment of disorders and diseases of the oral cavity, the stable, mucoadhesive gel formulations may be taken by mouth and distributed throughout the oral cavity by the action of the tongue and/or use of a swab or similar device. Excess gel can either be swallowed or expelled.

[0164] For treatment of disorders and diseases of the esophagus, the stable mucoadhesive liquid and gel formulations can be swallowed with minimal contact of the oral cavity, or administered by gavage, or by spraying the liquid into the throat.

[0165] For treatment of disorders and diseases of the nasal cavity, the stable mucoadhesive liquid and gel formulations can be delivered as droplets or by spraying the liquid into the nose.

[0166] For treatment of disorders and diseases of the bladder, the stable, mucoadhesive liquid or gel formulations of the current disclosure can be delivered by intravesical administration.

[0167] For treatment of disorders and diseases of the rectum and lower gastrointestinal tract, the stable mucoadhesive liquid or gel formulations can be administered by catheter or enema.

[0168] Other methods to apply the stable, viscous, mucoadhesive liquid formulations and stable mucoadhesive gel formulations of the current disclosure to mucosal tissues are known to those skilled in the art.

Kits

[0169] Also provided is a kit containing a formulation as described herein and instructions for use. In one aspect, the one or more medicinal food, nutritional supplement, therapeutic or prophylactic agent are separately packed for mixing just prior to administration. Instructions for use are optionally provided therein.

[0170] The following examples are intended to illustrate the various aspects of this disclosure.

EXAMPLES

Example 1. Preparation of basic, viscous, mucoadhesive aqueous ferrous sulfate composition

[0171] A viscous, mucoadhesive aqueous solution is formulated by adding Carbopol® 971P NF to water using an appropriate mixing apparatus (Master Servodyne® mixer with high-lift blade rotating at 200 - 300 rpm) to give a clear solution. An aqueous solution of potassium hydroxide is added with stirring to give a clear gel. An aqueous solution of ferrous sulfate, citric acid, saccharin sodium, phosphoric acid and glycerin are added with stirring to give a clear solution. A solution of benzyl alcohol and polysorbate 60 is added with stirring to give a clear solution. The pH is adjusted to 7.0 - 7.8 with aqueous solutions of phosphoric acid and potassium hydroxide. The resulting product is mixed further for 30 minutes.

[0172] The formulation of the product is set out in the following table:

Ingredients	Weight Percent
Carbopol® 971P	0.35
citric acid	0.05
polysorbate 60	0.05
10% potassium hydroxide	~4.60
benzyl alcohol	1.50
0.5% phosphoric acid	~5.70
Glycerin	5.00
saccharin sodium	0.40
ferrous sulfate heptahydrate	0.25%
purified water	q.s. 100%

Example 2. Preparation of viscous, mucoadhesive aqueous compositions containing nutritional supplements

[0173] The method set out in Example 1 is followed to provide a viscous, mucoadhesive aqueous composition containing ≤ 5% of one or more nutritional supplements, as follows:

[0174] Water-soluble vitamins: thiamine (vitamin B1), riboflavin(vitamin B2), niacin (vitamin B3), pantothenic acid, biotin, pyridoxine (vitamin B6), folic acid, cobalamin (vitamin B12), and ascorbic acid (vitamin C) fat-soluble vitamins: vitamins A, D, E, and K, formulated with a suitable emulsifying agent such as agar, albumin, alginates, casein, cetyl alcohol, cholic acid, desoxycholic acid, glycerol, lecithin, mono- and diglycerides, sodium stearate, propylene gycol, sodium taurocholate, or similar.

[0175] Minerals such as calcium (2+), chromium (3+), iron (2+ and 3+), magnesium (2+), and zinc (1+) in medically-acceptable salt forms.

Example 3. Preparation of additional viscous, mucoadhesive aqueous ferrous sulfate composition

[0176] The method set out in Example 1 is followed but using one of the formulations listed in the following table to provide a viscous, mucoadhesive aqueous composition containing 2.5% of ferrous sulfate as a nutritional supplement.

Ingredients	Formulations								
	1	2	3	4	5	6	7	8	9
50mM glycine/NaOH buffer	70%	70%	0%	0%	70%	70%	70%	0%	0%
boric acid/NaOH buffer	0%	0%	70%	70%	0%	0%	0%	0%	0%
Glycerine	2.5%	2.5%	2.5%	2.5%	2.5%	5%	5%	5%	5%
Noveon AA1	1.0%	1.0%	1.0%	1.0%	1.0%	0%	0%	0%	0%
Carbomer 971P	0%	0%	0%	1.0%	1.0%	1.0%	1.0%	1.0%	1.0%
Eudragit L100	0.1%	0%	0%	0%	0%	0%	0%	0.1%	0.1%
Ethanol	5.0%	0%	5.0%	0%	5.0%	0%	5.0%	0%	5.0%
phenoxyethanol	1.0%	1.0%	1.0%	0%	1.0%	0%	0%	0%	1.0%
benzyl alcohol	0%	0%	0%	1.5%	0.5%	1.5%	1.5%	1.5%	1.5%
polysorbate-60	0%	0%	0%	0%	0.05%	0.05%	0.05%	0.05%	0.05%
citric acid	0.05%	0%	0.05%	0.%	0.05%	0.05%	0%	0.05%	0.05%
PEG-20,000	0%	0%	0%	0%	0%	0.3%	0.3%	0%	0%
10% KOH solution	0%	0%	0%	0%	0%	0%	0%	~5.0%	~5.0%
10% Phosphoric acid	0%	0%	0%	0%	0%	0%	0%	~5.0%	~5.0%

sodium saccharin	0.4%	0%	0.4%	0%	0%	0.4%	0%	0.4%	0%
ferrous sulfate heptahydrate	2.5%	2.5%	2.5%	2.5%	2.5%	2.5%	2.5%	2.5%	2.5%
Water	qs 100%	qs 100%	qs 100%	qs 100%	qs 100%	qs 100%	qs 100%	qs 100%	qs 100%

Example 4. Preparation of additional viscous, mucoadhesive aqueous nutritional supplement compositions.

[0177] The method set out in Example 1 is followed but using one of the formulations listed in the table of Example 3 with one or more of the nutritional supplements listed in Example 2 replacing ferrous sulfate to provide a viscous, mucoadhesive aqueous composition containing ≤5% a nutritional supplement formulation.

Example 5. Preparation of viscous, mucoadhesive aqueous composition containing thiamine (vitamin B1) and amlexanox

[0178] A viscous, mucoadhesive aqueous solution is formulated by adding Carbopol® 971P NF to water using an appropriate mixing apparatus (Master Servodyne® mixer with high-lift blade rotating at 200-300 rpm) to give a clear solution. An aqueous solution of potassium hydroxide is added with stirring to give a clear gel. An aqueous solution of potassium hydroxide, citric acid, saccharin sodium, amlexanox, thiamine, phosphoric acid and glycerin is added with stirring to give a clear solution. A solution of benzyl alcohol and polysorbate 60 is added with stirring to give a clear solution. The pH is adjusted to 7.0-7.8 with an aqueous solution of phosphoric acid. The resulting product is mixed further for 30 minutes. The formulation of the product is set out in the following table:

Ingredients	Weight Percent
Carbopol® 971P	0.35
citric acid	0.05

polysorbate 60	0.05
10% potassium hydroxide	~4.60
benzyl alcohol	1.50
0.5% phosphoric acid	~5.70
Glycerin	5.00
saccharin sodium	0.40
Thiamine	0.05%
Amlexanox	1.5%
purified water	q.s. 100%

Example 6. Preparation of viscous, mucoadhesive aqueous composition containing thiamine, amlexanox and vitamin B12-coated nanoparticles of exenatide

[0179] Synthesis of VB12-Stearamide: To a suspension of stearic acid (1.0 g) and NHS (445 mg) in dichloromethane (50 mL) was added EDAC (740 mg) and the mixture is stirred for 24 hours at room temperature. The solution was washed with ice-cold water (3 x 50 mL), dried over Na_2SO_4 and evaporated under vacuum to afford stearic acid NHS ester as a white solid (1.2 g). To a solution of aminohexyl-VB12 (100 mg; JF McEwan et al, Bioconjugate Chemistry, 1999, 10, 1131-1136) in DMF (5 mL) was added triethylamine (5 drops), followed by a solution of stearic acid NHS ester (35.5 mg) in DMF (2 mL). The solution was stirred for 5 hours, then added to ethyl acetate (50 mL) and the resulting precipitate was centrifuged, washed with ethyl acetate (2 x 25 mL) and dried under high vacuum to afford stearamidohexyl-VB12 (VB12-Stearamide) as a red solid (102 mg).

[0180] Synthesis of VB12-coated PLGA nanoparticles containing exenatide: 100 µL of 10 mg/mL exenatide solution in pH 7.5 TE buffer was briefly combined with 200 µL of 20 mg/mL acetylated Bovine Serum Albumin solution, also in pH 7.5 TE buffer. 750 µL of RG 502H PLGA in dichloromethane was then added and the mixture was sonicated for 1 min. To the resulting white emulsion was added 2 mL of 20 mg/mL PVA solution (10k MW, 80% hydrolyzed), with sonication for an additional 1 min. This emulsion was then added to 12 mL of 20 mg/mL PVA solution, and the mixture stirred in an uncapped 20 mL vial for 1.5 h. It

was then centrifuged at 10,500 rpm for 20 min at 4°C and the supernatant decanted. The pellet was washed with deionized water (2 x 5 mL) and lyophilized to yield 16.3 mg of nanoparticles; Z-average = 210 nm, PDI = 0.092; Zeta potential = -35.9 mV. A 7 mL vial was charged with 9.0 mg of dried nanoparticles and 2 mL deionized water added with shaking for 15 min. To the resulting white suspension was added 100 μL of 1 mg/mL VB12-Stearamide solution in EtOH and the mixture was shaken for 48 h, then centrifuged at 13,000 rpm for 30 min. The supernatant was decanted and the pellet lyophilized to yield 10.2 mg of pink nanoparticles; Z-average = 266 nm, PDI = 0.196; zeta potential = -33.3 mV.

[0181] Immediately prior to administration to a patient, 10mL of the viscous mucoadhesive liquid of Example 5 is mixed with 500mg of dried nanoparticles from 'b' above, and the mixture is administered orally to a patient.

Example 7. Vitamin B12 targeted conjugate of resveratrol

[0182] Aminohexyl-VB12 (see example 6) can be conjugated to succinoyl resveratrol (L.Biasutto et al, Bioorg Med Chem Lett. 2009, 19(23), 6721-4) by amide coupling methods known in the art, for example, use of the coupling reagent EDAC.

Example 8. Vitamin B12 targeted conjugate of vitamin E

[0183] Aminohexyl-VB12 (see example 6) can be conjugated to succinoyl α-tocopherol (BM Folmer et al, Biochem Pharmacol. 2009, 78(12),1464-74) by amide coupling methods known in the art, for example, use of the coupling reagent EDAC.

Example 9. Vitamin B12 targeted nanoparticle of vitamin E

[0184] Synthesis of 70 kDa Carboxymethyl Dextran. A solution of 70 kDa dextran (4.0 g) in 11% sodium hydroxide (20 mL) was added to a solution of chloroacetic acid (2.3 g) in tert butanol (40 mL) and the biphasic mixture was stirred vigorously at 60°C for 3 hours. After cooling to room temperature, the mixture was poured into stirring acetone (400 mL) and the resulting pasty precipitate was separated by decantation. The paste was dissolved in water (25 mL) and poured into stirring methanol (300 mL) and the resulting white precipitate was filtered, washed with methanol and dried under vacuum. The crude product was dissolved in water and 5x diafiltered with water using a 0.1 m2 TFF (tangential flow filtration) module with a 5 kDa MWCO membrane. The solution was then concentrated by TFF and lyophilized

to afford a white solid (4.6 g). 1H NMR analysis revealed that the product contained 0.2 carboxy-methyl equivalents per anhydroglucose unit (20% carboxymethylation).

[0185] Synthesis of 70 kDa VB12-Aminoethylamido-Carboxymethyl Dextran Conjugate. 20% Carboxymethyl 70 kDa dextran (200 mg) and aminohexyl-VB12 (75 mg) were dissolved in water (10 mL). 1-Ethyl-3-(3-dimethylaminopropyl) carbodiimide hydrochloride (EDAC; 60 mg) and N hydroxysuccinimide (NHS; 15 mg) were added and the solution was stirred for 4 hours at pH 5.3-5.7. Ethylenediamine dihydrochloride (164mg) and a further portion of EDAC (176 mg) were added, the pH was adjusted to pH 5.6 and the reaction was stirred overnight. The mixture was centrifuged in a 5 kDa Amicon 15 centrifugal filter at 3800 rpm for 30 min. Water (15 mL) was added to the retentate and centrifuged, and then the 15 mL wash was repeated twice more. The retentate was lyophilized to afford Cob-EDCMD70 (170 mg) as a pale red solid. UV-VIS spectrophotometric analysis revealed the product contained 6.5% w/w of VB12, which corresponds to 0.9 equivalents of VB12 per 100 anhydroglucose units (0.9 mol% VB12).

[0186] Vitamin B12 targeted nanoparticle of vitamin E. An aqueous solution of the above VB12 derivative dextran conjugate can be added to a solution of vitamin E (α-tocopherol) in a water-miscible solvent and the mixture agitated gently for 1 hour at room temperature, then lyophilized. VB12-targeted vitamin E nanoparticles will be obtained as a pale red solid.

Example 10. Vitamin B12 targeted nanoparticle of resveratrol

[0187] A vitamin B12 targeted nanoparticle can be produced by the method described in example 9 replacing vitamin E with resveratrol.

Example 11. Vitamin B12 targeted nanoparticle of conjugated resveratrol

[0188] Succinoyl resveratrol (from example 7) can be converted to its N-hydroxysuccinimide (NHS) ester and coupled to the VB12 dextran derivative of Example 9b, and this targeted conjugate formulated and used directly for delivery of resveratrol to a patient, or converted to nanoparticles as described in Example 9c using a suitable mixture of water and water-miscible solvent.

Example 12. Stability Study

[0189] Stability of the compositions or formulations can be determined as follows. A gel or liquid is packaged in clear glass bottles which are sealed, e.g., with white screw caps fitted

with teflon liners. The bottles are divided into two groups. One group is stored in a stability chamber set at 25 °C / 60% relative humidity, while the second group is stored at 40°C / 75% relative humidity. Bottles are examined at 0, 1, 2, 3, and 6 months for physical appearance (clarity of the solution), package integrity, amlexanox and benzyl alcohol contents, pH, and viscosity. At all times and under both conditions, no physical or chemical changes were noted.

Example 13. Rheology study

[0190] A Brookfield viscometer can be used to determine the rheological behavior of the formulation at various temperatures, e.g., 25 +/- 1 °C or 37 +/-1 °C. A rheogram can be generated by progressively increasing RPM, from 0.3 up to 60 RPM (upcurve) recording the % Torque after each reading stabilized. The upcurve is immediately followed by a downcurve, from 60 RPM to 0.3 RPM. Viscosity is calculated at each RPM, and the stress is then determined by multiplying the viscosity by the RPM. The rheological profile is generated by plotting stress (e.g., F/A) on the x-axis and RPM (e.g., Rate of Shear) on the y-axis.

Example 14. Clinical study

[0191] For the treatment of oral or throat lesions, a clinical study can be conducted in patients 18 years of age or older with a histologically documented diagnosis of head-and-neck cancer and a KPS of at least 60%, who received a radiation dose of at least 60 Gy over 6-7 weeks with radiation fields to include at least 40% of the oral mucosa. Patients receiving concomitant chemotherapy may also be included in the study. The patients will rinse using a disclosed formulation for up to 6 times a day (5 mL each time) for the duration of the radiation treatment (6-7 weeks), beginning on the first day of radiation therapy. An objective measurement of the degree of mucositis (the "Sonis Scale", described in Cancer, 1999, 85(10) 2103-13) can be made three times a week for the duration of the study.

[0192] Although several embodiments of the disclosure are described herein in detail, it will be understood by those skilled in the art that variations may be made thereto without departing from the spirit of the invention or the scope of the appended claims.

[0193] The embodiments illustratively described herein may suitably be practiced in the absence of any element or elements, limitation or limitations, not specifically disclosed herein. Thus, for example, the terms “comprising”, “including,” “containing”, etc. shall be

read expansively and without limitation. Additionally, the terms and expressions employed herein have been used as terms of description and not of limitation, and there is no intention in the use of such terms and expressions of excluding any equivalents of the features shown and described or portions thereof, but it is recognized that various modifications are possible within the scope of the invention claimed.

[0194] Thus, it should be understood that although the present disclosure has been specifically disclosed by preferred embodiments and optional features, modification, improvement and variation of the embodiments herein disclosed may be resorted to by those skilled in the art, and that such modifications, improvements and variations are considered to be within the scope of this disclosure. The materials, methods, and examples provided here are representative of preferred embodiments, are exemplary, and are not intended as limitations on the scope of the disclosure.

[0195] The disclosure has been described broadly and generically herein. Each of the narrower species and subgeneric groupings falling within the generic disclosure also form part of the disclosure. This includes the generic description of the disclosure with a proviso or negative limitation removing any subject matter from the genus, regardless of whether or not the excised material is specifically recited herein.

[0196] In addition, where features or aspects of the disclosure are described in terms of Markush groups, those skilled in the art will recognize that the disclosure is also thereby described in terms of any individual member or subgroup of members of the Markush group.

[0197] All publications, patent applications, patents, and other references mentioned herein are expressly incorporated by reference in their entirety, to the same extent as if each were incorporated by reference individually. In case of conflict, the present specification, including definitions, will control.

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WHAT IS CLAIMED IS:

1. A supplement formulation, comprising a mucoadhesive and an effective amount of one or more of a medicinal food or a nutritional supplement.

2. The supplement of claim 1, wherein the supplement is formulated as a liquid or a gel.

3. The supplement of claim 1, further comprising an effective amount of a viscosity-inducing agent.

4. The supplement of any one of claims 1 to 3, wherein the medicinal food and/or nutritional supplement is covalently linked directly to a targeting moiety or by a linker.

5. The supplement of any one of claims 1 to 4, further comprising an effective amount of one or more of a therapeutically or prophylactically active drug.

6. The supplement of any one of claim 5, wherein one or more of the therapeutically active drug, the prophylactically active drug, the medicinal food or the nutritional supplement is encapsulated within a nanoparticle.

7. The supplement of claim 5, wherein the nanoparticle further comprises a targeting moiety.

8. The supplement of claim 7, wherein the targeting moiety comprises a B vitamin .

9. The supplement of claim 8, wherein the B vitamin is one or more of folic acid, biotin, or vitamin B12 .

10. The supplement of any one of claims 3 to 9, wherein the mucoadhesive and the viscosity inducing agent are the same or different.

11. The supplement of any preceding claim, wherein the mucoadhesive is a linear or a cross-linked polymer.

12. The supplement of claim 11, wherein the mucoadhesive is one or more of a linear or cross-linked polymer of the group: polyacrylic acid, carboxymethylcellulose, hydroxyalkyl cellulose, dextran sulfate, dermatan sulfate, a water-soluble vinyl polymer or chitosan.

13. The supplement of any preceding claim, wherein the mucoadhesive comprises a single mucoadhesive component or a mixture of different mucoadhesive components.

14. The supplement of any preceding claim, wherein the mucoadhesive is at a concentration of about 0.10 w/w% to about 3.0 w/w%.

15. The supplement of any preceding claim, wherein the mucoadhesive is a Carbopol®.

16. The supplement of claim 15, wherein the Carbopol® is Carbopol 971®P.

17. The supplement of any one of claims 3 to 12, wherein the viscosity enhancer is one or more of agar, bentonite, glycerin, providone, kaoline, tragacanth, sodium alginate, or cross-linked polyacrylic acids.

18. The supplement of any one of claims 3 to 17, wherein the viscosity enhancer is glycerin.

19. The supplement of any one of claims 3 to 14, wherein the mucoadhesive is Carbopol and the viscosity enhancer is glycerin.

20. The supplement of any preceding claim, wherein the supplement is a liquid having a final pH of between about 3 to 9.

21. The supplement of any preceding claim, wherein the supplement is formulated as a pseudoplastic liquid.

22. The supplement of any preceding claim, further comprising a pharmaceutically effective drug for treating or preventing a mucocutaneous disorder.

23. The supplement of claim 22, where the mucocutaneous disorder is mucositis, Behcet's disease, apthous ulcer, bullous pemphigoid, chemical cystitis, radiation cystitis, erythema multiforme, cancer, esophagitis, interstitial cystitis, oral lichen planus, pemphigus, radiation proctitis, or ulcerative colitis.

24. A method for delivering one or more medicinal food and/or nutritional supplement comprising contacting the mucocutaneous surface of a subject with an effective amount of the supplement of any preceding claim.

25. The method of claim 24, wherein the mucocutaneous surface is one or more of the oral cavity, nasal cavity, gastrointestinal tract, respiratory tract, urinary tract, bladder, vagina, or rectum.

26. The method of claim 24 or 25, wherein the mucocutaneous surface is an oral cavity and the contacting is by gargling or swishing the supplement in the oral cavity by the subject or by the subject adopting a slow circulating movement of the subject's head.

27. A method for delivering a therapeutic agent, comprising administering to the subject in need of such agent an effective amount of any one of claims 5 to 24.

28. The method of claim 27, wherein mucocutaneous surface is an oral cavity and the administration to the subject is by gargling or swishing the supplement in the oral cavity by the subject or by the subject adopting a slow circulating movement of the subject's head.

29. A kit comprising an effective amount of the supplement of any one of claims 1 to 3, and optionally one or more therapeutically or prophylactically active drug encapsulated within a nanoparticle and instructions for use.

30. The kit of claim 29, wherein one or more of the medicinal food, nutritional supplement, therapeutically or prophylactically active drug are separately packed for mixing just prior to administration.

31. A medically-suitable nanoparticle system comprising an effective amount of one or more of a medicinal food or a nutritional supplement.

32. The nanoparticle of claim 31, further comprising a pharmaceutically active agent

33. The nanoparticle of claim 31, further comprising one or more targeting groups linked to the surface of the nanoparticle, wherein the targeting groups may be the same or different.

34. The nanoparticle of claim 33, wherein the targeting group comprises a B vitamin.

35. The nanoparticle of claim 34, wherein the B vitamin is one or more of folic acid, biotin, or vitamin B12.

36. A targeted conjugate comprising one or more of a medicinal food or a nutritional supplement covalently joined to a targeting group, and optionally comprising a stable or degradable linker, joining the targeting group and the one or more medical food or nutritional supplement.

37. The targeted conjugate of claim 36, wherein the targeting group comprises a B vitamin.

38. The targeted conjugate of claim 37, wherein the B vitamin is one or more of folic acid, biotin, or vitamin B12.

39. A pharmaceutical formulation comprising the supplement of claim 5, the nanoparticle of any one of claims 33 to 35, or the conjugate of claims 36 to 38, formulated as a pharmaceutically-acceptable solid, liquid or gel.

40. A method for treating a mucocutaneous surface or a mucocutaneous disorder in a subject, comprising administering to the subject in need thereof, an effective amount of the supplement of claim 5, the nanoparticle of any one of claims 33 to 35, the conjugate of claims 36 to 38, or the formulation of claim 39, thereby treating the subject.

41. The method of claim 40, wherein the mucocutaneous disorder is mucositis, Behcet's disease, apthous ulcer, bullous pemphigoid, chemical cystitis,

radiation cystitis, erythema multiforme, cancer, esophagitis, interstitial cystitis, oral lichen planus, pemphigus, radiation proctitis, or ulcerative colitis.

42. A method for preparing a supplement, comprising admixing an effective amount of a one or more of a medicinal food or a nutritional supplement and a mucoadhesive polymer.

43. The method of claim 42. further comprising admixing an effective amount of a viscosity-inducing agent.

44. The supplement of claim 42 or 43, wherein the medicinal food and/or nutritional supplement is covalently linked directly to a targeting moiety or by a linker.

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2015/016196

A. CLASSIFICATION OF SUBJECT MATTER
INV. A61K47/48 A61K9/00 A61K9/06 A61K9/19 A61K9/51
ADD.

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

B. FIELDS SEARCHED

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

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

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
EPO-Internal, CHEM ABS Data, EMBASE, WPI Data, BIOSIS, FSTA

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	FEDERICA SARTI ET AL: "Poly(acrylic acid)-cysteine for oral vitamin B12 delivery", ANALYTICAL BIOCHEMISTRY, vol. 420, no. 1, 1 January 2012 (2012-01-01), pages 13-19, XP55181494, ISSN: 0003-2697, DOI: 10.1016/j.ab.2011.08.039	1,5,7-9, 11-13, 21-27, 38-42
Y	abstract	1-43

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

[X] See patent family annex.

* Special categories of cited documents :

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

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

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

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
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Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Schüle, Stefanie

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INTERNATIONAL SEARCH REPORT

International application No
PCT/US2015/016196

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	C. JACOBS ET AL: "Production and characterisation of mucoadhesive nanosuspensions for the formulation of bupravaquone", INTERNATIONAL JOURNAL OF PHARMACEUTICS, vol. 214, no. 1-2, 1 February 2001 (2001-02-01), pages 3-7, XP55181490, ISSN: 0378-5173, DOI: 10.1016/S0378-5173(00)00622-0	1-3,5,6, 10-14, 19-24, 26, 28-31, 38-42
Y	abstract	1-43

X	US 2012/231069 A1 (NOWOTNIK DAVID P [US] ET AL) 13 September 2012 (2012-09-13)	1,4-11, 13,21, 23,24, 26, 28-39, 41-43
Y	claim 1 pages -; examples page 8, paragraph 0077	1-43

X	US 2003/060486 A1 (JACOB JEREMY E [US] ET AL) 27 March 2003 (2003-03-27)	1-3, 10-24, 26,41,42
Y	examples	1-43

X	LEE WEN-FU ET AL: "Effect of bentonite on the physical properties and drug-release behavior of poly(AA-co-PEGMEA)/bentonite nanocomposite hydrogels for mucoadhesive", JOURNAL OF APPLIED POLYMER SCIENCE, NEW YORK, NY, US, vol. 91, no. 5, 5 March 2004 (2004-03-05), pages 2934-2941, XP002453766,	1-3, 10-14, 17,19, 20,23-25
Y	Drug-release experiment; page 2937 page 2939, column 2, paragraph 2	1-43

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INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/US2015/016196

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 2012231069 A1	13-09-2012	CN 103501821 A	08-01-2014
		EP 2683410 A2	15-01-2014
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		WO 2012122313 A2	13-09-2012
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