Abstract:
Calcium glycerophosphate is found to be effective in treating and preventing a disease, disorder and/or condition of the respiratory system. The disease, disorder and/or condition is related to an obstructive or a restrictive condition of the respiratory airway. The disease, disorder and/or condition can be a respiratory airway inflammatory disease, a respiratory airway stenosis or a nasal cavity inflammatory disease, such as an asthma, a chronic obstructive pulmonary disease (COPD), an emphysema, a reactive airway disease (RADS), rhinitis, bronchitis, bronchiolitis, congestion, sinusitis, tonsillitis, or laryngitis, post-nasal drip (PND) and a related complication thereof, inflamed degranulating and non-degranulating mast cell activity, any irritation occasioning mucus secretion from goblet cells breathing difficulty, restriction, obstruction, airways constriction or closure or mucus interference with air passage, sleep apnea, snoring, inflammatory or non-inflammatory responses to an airborne or non-airborne allergen or irritant.
Calcium Glycerophosphate for Treating and Preventing Respiratory Diseases or Conditions

BACKGROUND OF THE INVENTION

[0001] Diseases, disorders and/or conditions of the respiratory system occur commonly in both affluent countries and developing countries. They account for a significant proportion of all days of sickness related absence from work. The morbidity related to respiratory diseases, disorders and conditions has not decreased.

[0002] Therefore, there is a need to develop a relatively inexpensive means for treating and preventing diseases, disorders and/or conditions of the respiratory system. Preferably, such a means is non-toxic, non-hazardous and without significant side effects.

BRIEF SUMMARY OF THE INVENTION

[0003] It is now discovered that calcium glycerophosphate is effective in treating and preventing a disease, disorder and/or condition of the respiratory system.

[0004] In one general aspect, the present invention relates to a method of treating or preventing a disease, disorder and/or condition of the respiratory system in a subject. The method comprises administering to the respiratory system of the subject an effective amount of calcium glycerophosphate in a composition formulated for oral or nasal administration.

[0005] In another general aspect, the present invention relates to a composition for treating or preventing a disease, disorder and/or condition of the respiratory system in a subject. The composition comprises an effective amount of calcium glycerophosphate and is formulated for oral or nasal administration to the respiratory system of the subject by a nasal drop, a nasal spray, a gel, a nasal lavage, a quick-dissolving tablet, an inhaled powder, an oral inhalation solution or suspension, a syrup, a mechanized intermittent fluid pulser (such as Water-Pik®), an inhaler, a respirator, a transpirator, an atomizer, a vaporizer, a nebulizer, an air mask, an insufflator, a means for direct physical or mechanical application (such as a cotton swab), etc.

[0006] In yet another general aspect, the present invention relates to a device for treating or preventing a disease, disorder and/or condition of the respiratory system in a subject. The device comprises an effective amount of calcium glycerophosphate and a means for administering the effective amount of calcium glycerophosphate to the respiratory system of the subject.
[0007] Other aspects, features and advantages of the invention will be apparent from the following disclosure, including the detailed description of the invention and its preferred embodiments and the appended claims.

DETAILED DESCRIPTION OF THE INVENTION

[0008] Calcium glycerophosphate has already been shown to behave as an anti-inflammatory substance on epidermal and epithelial cells and as a wound healer on epidermal cells as well as in the gums and mucosal soft tissue elsewhere in the body, e.g., vaginal. Investigation has been expanded to its use on the nasal mucosa and other parts of the respiratory system.

[0009] Unless defined otherwise, all technical and scientific terms used herein have the same meaning as commonly understood to one of ordinary skill in the art to which this invention pertains. Otherwise, certain terms used herein have the meanings as set in the specification. All patents, published patent applications and publications cited herein are incorporated by reference as if set forth fully herein. It must be noted that as used herein and in the appended claims, the singular forms "a," "an," and "the" include plural reference unless the context clearly dictates otherwise.

[0010] As used herein, the term "subject" refers to a mammal, who has been the object of treatment, observation or experiment. Examples of a subject can be a human, a livestock animal (beef and dairy cattle, sheep, poultry, etc.), or a companion animal (dog, cat, horse, etc).

[0011] As used herein, the term "respiratory system" refers to all parts of the airway, i.e., the passageway for air during respiration, from the nose to the pulmonary alveoli. The respiratory system includes organs that are involved in breathing, such as the nose, throat, larynx, trachea, bronchi, and lungs.

[0012] As used herein, the term a "disease, disorder and/or condition of a/the respiratory system" refers to any disease, disorder and/or condition that is related to an obstructive or restrictive condition of a respiratory system. An obstructive condition of a respiratory system includes any condition which impedes the rate of air flow into and out of the lung. A restrictive condition of a respiratory system includes any condition which causes a reduction in the functional volume of the lung. The obstruction or restriction of the airway may cause symptoms such as wheezing, shortness of breath, difficulty breathing, chest tightness, and coughing. The disease, disorder and/or condition of the respiratory system can be, for example, an airway inflammatory disease, an airway stenosis, or a nasal cavity inflammatory disease.

[0013] Examples of the disease, disorder and/or condition of the respiratory system include, but are not limited to, an asthma; a chronic obstructive pulmonary disease (COPD); an emphysema, a
reactive airway disease (RADS); rhinitis; bronchitis; bronchiolitis; congestion; sinusitis; tonsillitis; laryngitis; post-nasal drip (PND) and any and all complications dependent on same; inflamed degranulating and non-degranulating mast cell activity; any irritation occasioning mucus secretion from goblet cells or elsewhere, resulting in breathing difficulty, restriction and/or obstruction; airway constriction or closure or mucus interference with air passage; sleep apnea; snoring; inflammatory or non-inflammatory responses to any airborne or other allergen or irritant; nasal or other airway inflammation or irritation caused by any other body area problem; physical damage to the respiratory system such as nosebleed, surgery healing, traumatic injury; any respiratory disease, disorder and/or condition caused by an airborne or seasonal allergen or irritant, any swelling of tissue occasioned by any of the above, etc.

[0014] As used herein, the term "asthma" refers to a chronic condition, which in most cases is characterized by reversible airway obstructions and/or constrictions. The airway becomes inflamed and is lined with excessive amounts of mucus, often in response to one or more triggers for asthma. The triggers for asthma include, but are not limited to, an environmental stimulant, such as an allergen (ragweed, house dust, animal hair, pollen, etc.), cold air, warm air, moist air, change in temperature or humidity, upper respiratory infections, exercise, exertion, physical or emotional stress, smoke, viral illnesses such as those caused by common cold. The term "asthma" includes those caused by any cause of asthma whose primary effect is cellular inflammation and/or irritation, whether involving mast cells or not, degranulation or not, mucus exudation or not, whether exacerbant is identified or not, or whether the cause is airborne or not. The term 'asthma' is to be the widest-encompassing and is to include breathing difficulty of all degrees from the barely perceptible to acute.

[0015] Examples of asthma include, but are not limited to bronchial asthma, infantile asthma, allergic asthma, atopic asthma, steroid refractory asthma, non-allergic asthma, endogenous asthma, exogenous asthma, aspirin asthma, cardiac asthma, exercise-induced asthma, infectious asthma, any asthma triggered by airway restriction or constriction.

[0016] As used herein, the term "chronic obstructive pulmonary disease" or "COPD", also known as chronic obstructive airway disease (COAD), refers to a progressive respiratory disease characterized by limitation of airflow in the airway that is not fully reversible. COPD often involves permanent or temporary narrowing of small bronchi, in which forced expiratory flow is slowed. Examples of COPD include chronic bronchitis, emphysema and a range of other disorders to which no etiologic or other more specific term can be applied. COPD is most often due to tobacco
smoking but can be due to other airborne irritants, such as coal dust, asbestos or solvents, as well as preserved meats containing nitrates.

[0017] As used herein, the term "reactive airway disease (RAD)" refers to an asthma-like syndrome developed after a single exposure to high levels of a trigger, such as irritating vapor, fume, or smoke. In a particular embodiment of the present invention, the term RAD includes an asthma-like syndrome in infants that may later be confirmed to be asthma when they become old enough to participate in diagnostic tests.

[0018] As used herein, the term "rhinitis" refers to any disease, disorder and/or condition caused by inflammation of the nasal mucous membrane. Examples of rhinitis include, but are not limited to, allergic rhinitis, pollinosis, acute rhinitis, chronic rhinitis, hypertrophic rhinitis, deflected septum and the like. Symptoms of rhinitis include, but are not limited to, a runny nose, nasal congestion and post-nasal drip. According to recent studies completed in the United States, more than fifty million Americans are current sufferers of rhinitis. Rhinitis has been found to adversely affect more than just the nose, throat, and eyes. It has been associated with sleeping problems, problems with the ears, and has even been linked to learning problems. Causes that may bring about the presence of rhinitis include food reactions, anatomic defects, immunodeficiency diseases, ciliary dyskinesia, environmental triggers, emotional triggers, occupational triggers, hormonal triggers, etc.

[0019] As used herein, the term "calcium glycerophosphate" or "CGP," also known as "glycerophosphate calcium," refers to a chemical compound having a molecular formula of C$_3$H$_7$CaO$_6$P in its anhydrous form. "CGP" can also exist as a hydrate, including the monohydrate and the dihydrate. Examples of calcium glycerophosphate include, but are not limited to, any one, or any combination of two or more of the three isomers of CGP, namely β-glycerophosphoric acid calcium salt ((HOCH$_2$)$_2$CHOPC)$_3$Ca) and D(+) and L(−)-α-glycerophosphoric acid calcium salt (HOCH$_2$CH(OH)CH$_2$OPO$_3$Ca).

[0020] Calcium glycerophosphate can be synthesized using methods known in the art. Calcium glycerophosphate can also be obtained from various commercial sources. The commercially available CGP preparations include, but are not limited to, those available from AkPharma Inc. (Pleasantville, NJ 08232), Astha Laboratories Pvt, Ltd, (B-4, Industrial Estate, Sanathnagar, Hyderabad, 18, India), and Seppic Inc. (30 Two Bridges Road, Fairfield, NJ 07004).

[0021] As used herein the term "treatment", "treat" or "therapy" refers to the prevention of deterioration of a disease, disorder or condition when a patient contracts such a disease, disorder or condition, preferably, at least maintenance of the status quo, and more preferably, alleviation, still more preferably, resolution of the disease, disorder or condition.
As used herein the term "prophylaxis", "prevent" or "prevention" refers to, when referring to a disease, disorder or condition, a type of treatment conducted before such a disease, disorder or condition occurs such that the disease, disorder or condition will not occur, will be delayed to occur, or will occur but will deteriorate to a less degree.

As used herein, the term "treat" or "prevent" in the broadest sense, with respect to a disease, disorder or condition, refers to any medical act thereto, and include any act for diagnosis, therapy, prevention, prognosis and the like.

When used for treating or preventing a disease, disorder and/or condition of the respiratory system, calcium glycerophosphate can be used as a reliever which is used during an episode or an attack of the disease, disorder and/or condition, such as an episode of an asthma, for alleviation of the episode or attack. Calcium glycerophosphate can also be used as a controller which is used for long-term control to prevent the occurrence of the episode or attack. Controlling or preventing an attack is substantially the therapy of a disease, disorder and/or condition of the respiratory system per se, because it is equally important to control and prevent an attack as to relieve or alleviate the attack. Those skilled in the art will be able to use an appropriate dosage of calcium glycerophosphate for either therapy or prevention of a disease, disorder and/or condition of the respiratory system.

The term "effective amount" as used herein means that amount of active compound or pharmaceutical agent that elicits the biological or medicinal response in a tissue system, animal or human that is being sought by a researcher, veterinarian, medical doctor or other clinician, which includes alleviation of the symptoms of the disease or disorder being treated. The administration of an effective amount of calcium glycerophosphate to a subject results in a clinically observable beneficial effect. The clinically observable beneficial effect can be a situation in which an observable disease, disorder and/or condition of the respiratory system is prevented from further development or aggravation or will develop to a lesser degree, than without administration of the composition of the present invention. The clinically observable beneficial effect can also be a situation in which a disease, disorder and/or condition of the respiratory system is prevented from occurring or subsequently occurs to a lesser degree than without administration of the composition of the present invention, when the composition is administered to a subject before the disease, disorder and/or condition of the respiratory system is observable. In one embodiment of the invention, an effective amount of calcium glycerophosphate alleviates or improves a disease, disorder and/or condition of the respiratory system in a subject to a degree that is about any of 10%,
20%, 30%, 40%, 50%, 60%, 70%, 80%, or 90% of that which would have been had the subject not received an effective amount of calcium glycerophosphate.

[0026] Methods are known in the art for determining therapeutically and prophylactically effective doses of calcium glycerophosphate according to embodiments of the present invention. A useful assay for confirming an effective amount (e.g., a therapeutically effective amount) for a predetermined application is to measure the degree of recovery from a target disease. An amount actually administered depends on an individual to be treated. The amount is preferably optimized so as to obtain a desired effect without significant side effects. The determination of a prophylactically or therapeutically effective dose is within the ability of those skilled in the art. A prophylactically or therapeutically effective dose of any compound can be estimated using either a cell culture assay or any appropriate animal model. The animal model is used to achieve a desired concentration range and an administration route. Thereafter, such information can be used to determine a dose and route useful for administration into humans.

[0027] The therapeutic effect and toxicity of a compound may be determined by standard pharmaceutical procedures in cell cultures or experimental animals (e.g., ED$_{50}$, a dose therapeutically effective for 50% of a population; and LD$_{50}$, a dose lethal to 50% of a population). The dose ratio between therapeutic and toxic effects is a therapeutic index, and it can be expressed as the ratio of ED$_{50}$/LD$_{50}$. Pharmaceutical compositions which exhibit high therapeutic indices are preferable. The data obtained from cell culture assays and animal studies can be used for formulating a dosage range for use in humans. The dosage of such compounds lies preferably within a range of circulating concentrations that include the ED$_{50}$, with little or no toxicity. Such a dosage may vary within this range depending upon the dosage form employed, the susceptibility of a patient, and the route of administration. Guidance for specific doses and delivery methods is provided in publications known in the art. The exact dose is chosen by an individual physician in view of the condition of a patient to be treated. Doses and administration are adjusted to provide a sufficient level of the active portion, or to attain a desired effect.

[0028] The effective amount of CGP can be any dosage amount, from micro-doses to mega-doses. Mega-doses of CGP can be effectively used, because CGP is non-toxic, non-hazardous and has no known side effects. Micro-doses of CGP can be effectively used, because both Ca$^{2+}$ and the glycerophosphate anion are signaling molecules that can have a biological effect at very low levels.

[0029] In embodiments of the present invention, the effective amount of CGP is administered to the subject in a composition containing about 0.05% - 15% (w/w), preferably about 0.5% - 10% (w/w); most preferably about 1% - 5% (w/w) of CGP. It has been discovered that at higher levels
tested, e.g., about 7.5% (w/w) or above, calcium glycerophosphate may help in stanching nosebleeds, possibly due to the effect of calcium on blood clotting. However, the amount of CGP in the composition is not limited to about 0.05% - 15% (w/w).

[0030] In one general aspect, an embodiment of the present invention relates to a method of treating or preventing a disease, disorder and/or condition of a respiratory system in a subject. The method comprises administering to the respiratory system of the subject an effective amount of calcium glycerophosphate, wherein calcium glycerophosphate is administered to the respiratory system of the subject in a composition formulated for oral or nasal administration. The composition formulated for oral or nasal administration can be a liquid, solid, gel, syrup, powder, or mist formulation.

[0031] Calcium glycerophosphate can be administered to the respiratory system of the subject by one or more means of oral or nasal administration depending on the type of diseases, disorders and/or conditions of the respiratory system. For example, in the case of asthma, COPD and the like, atomizer type inhalators such as MDI, BDI, or nebulizers and the like may be used for inhalation. For example, in the case of rhinitis, absorption and inhalation may be used for administration. Examples of applicable means of oral or nasal administration include, but are not limited to, a nasal drop, a nasal spray, a nasal lavage, a quick-dissolving tablet, an inhaled powder, an oral inhalation solution or suspension, a syrup, a mechanized intermittent fluid pulser (such as Water-Pik®), an inhaler, a respirator, a transpirator, an atomizer, a vaporizer, an air mask, an insufflator, a means for direct physical or mechanical application, such as a cotton swab, etc.

[0032] Inhalation is conventionally used as a method for administration via the nasal cavity, airway and nasal pathways and the like. In intra-airway administration formulations, transairway absorption formulations or pernasal absorption formulations, it is usually preferable to make a drug solution in a mist form or as fine powder (dry powder). Generally, a drug solution formed may be inhaled by means of a nebulizer, those processed into powder may be inhaled by means of a gas-atomizing type, MDI (metered dose inhaler) or expiration inhalation system, DPI (dry powder inhaler) with the drug loaded therein.

[0033] With respect to powder inhalers, there are two types presently used for rapid and deep inhalation, "dry powder inhaler (DPI)" and delayed inhaling type "metered dose inhaler (MDI)". DPI are further classified into three categories: multi-dose reservoir, such as the product TURBUHALER®, available from AstraZeneca; multi-unit dose, such as the product ACCUHALER™/ FLOVENT DISKUS™, available from GSK; and unit dose, available from many manufacturers.
[0034] Inhaler refers to a kit comprising a mouth piece and cartridge (tube), and are usually employed by sealing both termini of the tube with aluminum foil. Prior to use, the tube is equipped with the mouth piece to pierce the aluminum foil, thereby allowing inspiration of powdered drug inside.

[0035] On the other hand, absorption of a drug solution may be achieved by means of a nebulizer or respirator, an artificial respirator. A nebulizer causes a drug aerosol to flow in the air at slow speed, thus makes it easier for one to absorb the drug.

[0036] How often and how long calcium glycerophosphate is administered to a subject depends on the disease, disorder and/or condition of the respiratory system to be treated or prevented, as well as factors associated with the subject, e.g., age, weight, health, etc. Calcium glycerophosphate can be administered on a regimen of one to multiple times per day. Calcium glycerophosphate can be administered to the subject at intervals during the day, such as upon arising, after breakfast, lunch, dinner, and upon retiring. Calcium glycerophosphate can be administered during an episode or an attack of the disease, disorder and/or condition of the respiratory system to provide a relief of symptoms, such as wheezing, shortness of breath, difficulty breathing, chest tightness, and coughing. Calcium glycerophosphate can also be administered to a subject prior to an episode or an attack to control or prevent the episode or attack and the symptoms associated with the episode or attack.

[0037] Dosages of calcium glycerophosphate are not limited to a particular value. The dosage appropriately varies depending on the targeted disease, condition (extent), age, the presence or absence of complication(s), etc. For example, the dosage is usually, per adult, per administration, about 100 µg to about 1000 mg, preferably about 500 µg to about 100 mg, and most preferably about 1 mg to about 40 mg of anhydrous CGP. As used herein, "anhydrous CGP" refers to a CGP preparation that contains at least about 88% (w/w) of CGP that is free of residual or acquired moisture. The anhydrous CGP used in embodiments of the present invention complies with Food Chemicals Codex (FCC) specifications, in which loss on drying (LOD) is not to exceed 12%. As used herein, "per administration" can be, per inhalation per nostril, per spray, per tablet, etc. In one embodiment of the present invention, the dosage is about 400 mg solution/suspension formulation containing about 2% by weight of dry CGP per administration. In another embodiment of the present invention, the dosage is about 400 mg solution/suspension formulation containing about 3.75% by weight of dry CGP per administration. The dry CGP contains about 95-98% anhydrous CGP balancing with moisture. However, the dosage of CGP is not limited to the above ranges and can be any range without causing physical endangerment.
While not wishing to be bound by theory, calcium glycerophosphate can be used to treat or prevent a disease, disorder and/or condition of the respiratory system at least in part due to the anti-inflammatory effect of CGP. Inflamed airway epithelium results in a disease, disorder and/or condition of the respiratory system. Various observations suggest that a glycerophosphate salt functions to promote epidermal cell renewal, see for example, US2004/0037766. The quick repair and replacement of epidermal cells provide, among other things, enhanced ceramide synthesis, which hastens repair of the skin's surface and provides tighter cell-to-cell adhesion, which may prevent invasion between vulnerable cell walls of irritating substances. This is to be distinguished from the possible function of the calcium ion to modify the permeability of cell membranes, per se, i.e., the ability of calcium ion to decrease membrane porosity at a large concentration. The reduction, interdiction, suppression or prevention of inflammation of the respiratory system provides symptom relief or prevention. The beneficial effect of CGP may also be due to, at least in part, its ability to prevent or reduce acid-caused irritation and cytotoxicity in the upper and lower respiratory tract, and/or its ability to promote higher ciliary activity, e.g., via regulating the phosphorylation state of certain ciliary proteins. It is believed that the newly discovered beneficial effect of CGP on the respiratory system according to embodiments of the present invention is achieved synergistically between the calcium ion and the glycerophosphate. This synergistic effect is distinct from the function of the calcium ion or the glycerophosphate alone.

Calcium glycerophosphate is non-toxic, non-hazardous and has no known side effects. Therefore, methods according to embodiments of the present invention are particularly desirable for pediatric patients, elderly patients, pregnant women, or patients who have frequent need of relief medications and/or preventive medications for a disease, disorder and/or condition of the respiratory system. Oral or nasal administration of the composition according to the present invention is non-invasive and can be repetitively provided.

In particular embodiments, calcium glycerophosphate can be administered in combination with one or more other relief and/or preventive agents for a disease, disorder and/or condition of the respiratory system. Thus, embodiments of the present invention relate to compositions comprising calcium glycerophosphate and one or more other relief and/or preventive agents for a disease, disorder and/or condition of the respiratory system, and methods of using the compositions for treating or preventing a disease, disorder and/or condition of a respiratory system in a subject. Calcium glycerophosphate and the other agent can be administered simultaneously or sequentially, one following the other. The other agents can be administered to the subject via routes of administration customarily used for such other drugs. However, it is not necessary to administer
the other relief and/or preventive agent in a substantial percentage of instances according to embodiments of the present invention. Calcium glycerophosphate, as the sole active pharmaceutical ingredient, is effective to treat or prevent a disease, disorder and/or condition of the respiratory system.

5 [0041] Examples of such relief and/or preventive agents include, but are not limited to, a beta-2 agonist, an alpha agonist, a bronchodilator, a glucocorticoid, a leukotriene modifier, a mast cell stabilizer, an antimuscarinic/anticholinergic, a methylxanthine, an antihistamine, omalizumab, methotrexate, and tianeptine, albuterol, cromolyn, or the like.

10 Other embodiments of the present invention may relate to compositions comprising calcium glycerophosphate and one or more analgesics, and methods of using the compositions to treat or prevent a disease, disorder and/or condition of a respiratory system in a subject. Examples of the compositions include, but are not limited to, a pharmaceutical product for treating a cold, hay fever, any respiratory disease, disorder and/or condition caused by an airborne or seasonal allergen or irritant, etc., comprising CGP as the nasal cleaner/decongestant (NasoCell™) and a common over the counter (OTC) analgesic such as ibuprofen, acetaminophen, aspirin, naproxen, capsaicin, etc.

15 The amount of CGP in the composition may be appropriate to supply in a single dosage, which may be 2 to 4 sprays of the NasoCell, to provide nasal cleaning and/or decongestant. The amount of the analgesic in the composition can be effective to relieve common headaches, sinus aches, eye aches, etc. that are associated with colds, hay fever, etc.

20 [0043] Nasal administration of the composition according to the present invention can provide more rapid relief of the symptoms associated with cold, hay fever, etc. Administration via nasal membrane absorption can be more quantitatively effective and more chronologically prompt to reach the bloodstream than the same analgesic ingested that must go through the gastric system for subsequent absorption with possible compositional compromise by the digestive process. In addition, the hypotonicity of the NasoCell allows the composition to adhere more readily to the epithelial nasal cells, thus be absorbed more readily through the cell walls and into the bloodstream.

25 [0044] The compositions according to the present invention offer the unique combination of effective nasal cleaning, nasal clearing, anti-inflammation, anti-swelling, and pain relief, without any of the psychogenic effects associated with the presently marketed drugs, such as diphenhydramine, ephedrine, pseudoephedrine, etc., nor any of the undesirable, typical anti- cholinergic side effects at the site or elsewhere in the body. The composition is safe to use liberally even when driving or operating machinery.
In another general aspect, an embodiment of the invention provides a composition for treating or preventing a disease, disorder and/or condition of the respiratory system in a subject. The composition comprises an effective amount of calcium glycerophosphate, wherein the composition is formulated for oral or nasal administration to the respiratory system of the subject by a nasal drop, a nasal spray, a nasal lavage, a quick-dissolving tablet, an inhaled powder, an oral inhalation solution or suspension, an inhaler, a respirator, a nebulizer, a transpirator, an atomizer, a vaporizer, an air mask, an insufflator, a means for direct physical or mechanical application, such as a cotton swab, etc.

The composition according to embodiments of the present invention may be produced using a method similar to methods known in the art, e.g., conventional mixing, dissolution, rendering to granules, preparation of a sugar-coated agent, elutriation, emulsification, capsule, inclusion, or freeze drying. One or more excipients can be added to the composition. Excipients which can be used are those that are inactive against calcium glycerophosphate, and as long as the use is recognized as a pharmaceutical additive, no limitation is made for such excipient. Examples of appropriate excipients include, but are not limited to, monosaccharides such as galactose, mannose, sorbose; disaccharides such as lactose, sucrose and trehalose and the like; polysaccharides such as starch, raffinose, dextran and the like; sugar alcohols (including glycerol, erythritol, arabitol, xylitol, sorbitol, mannitol); glycols (including ethylene glycol, propylene glycol, polyethylene glycol, polypropylene glycol); cellulose-like polymers (including hydroxy cellulose, hydroxy propyl cellulose); insoluble additives (crystalline cellulose, chitosan, calcium carbonate, talc, titanium oxide or silica (silicon oxide), and mixtures thereof.

The composition according to embodiments of the present invention can be formulated to have a pH of about 4.5 - 10, such as about 4.5 - 6.0, about 6.0 - 8.0, or about 8.0 - 10.0. Note that nasal pH varies considerably, from 4.5 - 6.5 in normal nasal cells, to as high as 8.3 in rhinitis. However, the pH of the composition according to embodiments of the present invention is not limited to the range of about 4.5 - 10, or that of the nasal pH.

The composition according to embodiments of the present invention can further contain a preservative. Preferably the preservative is food grade or pharmaceutical grade. Examples of appropriate preservatives include, but are not limited to, methylparaben, ethylparaben, butylparaben, propylparaben, sorbic acid and any other preservative that is typically used in water-based cosmetics, such as creams and lotions and some bath products. The preservative is preferably present at an amount that is sufficient to prevent the composition from supporting the growth of microbes, such as bacteria, fungi, or yeasts.
The composition according to embodiments of the present invention can also include an adhesion molecule or material that allows the composition to adhere to an airway tissue for an extended period of time, thus results in an extended release of CGP into the airway. Adherence is accomplished by a number of interactions, physical or chemical, such as electrostatic interaction, hydrogen bonding or hydrophobic interaction. In preferred embodiment, the adhesion molecule or material extends the contact time of CGP in the nasal cavity. Any suitable adhesion molecule or material known to a person skilled in the art can be used in a composition according to embodiments of the present invention. In one embodiment, the adhesion molecule or material is a polysaccharide. In a preferred embodiment, the adhesion molecule is chitosan, a cationic polysaccharide derived from the shells of crustaceans. A versatile transmucosal delivery system based on chitosan is commercially available from West Drug Delivery of Lionville, PA 19353 (US), and can be used in the present invention.

In a preferred embodiment, the composition of the present is formulated as a powder, gel, microsphere, or suspension, i.e., liquid comprising CGP in an amount exceeding the solubility of CGP in the liquid. CGP has limited solubility in water, i.e., about 1% by weight. Administration of CGP in a formulation of powder, gel, microsphere, or suspension can result in a local amount of CGP exceeding its solubility, thus deposition of insoluble CGP onto the mucous membranes of the respiratory system. As the insoluble CGP slowly dissolves into mucous membranes, an extended release of CGP into the cells lining the airway is achieved without the need for any additional assisting adhesion substances. Optionally, the powder, gel, microsphere, or suspension formulation can include an adhesion molecule, a "sticker", or material that further enhances the CGP’s adherence to the airway mucosal surface.

A formulation that provides an extended release of CGP is preferred, for example, when it is desirable to provide a sustained and steady state level of CGP into the respiratory system for an extended time period, such as when the formulation is used for prophylaxis. In one embodiment, a method according to embodiments of the invention comprises administering to the respiratory system of the subject a formulation that provides an extended release of CGP into the airway. In a preferred embodiment, the CGP is released into the airway during a time period of 3-8 hours.

In another embodiment, a composition according to embodiment of the present invention comprises an absorption enhancer that improves absorption of CGP into the airway, e.g., across the mucous membranes of the airway. There are a number of ways an absorption enhancer can act. For example, it may alter properties of the mucus layer by opening tight junctions between the cells, or it may increase membrane fluidity. Any suitable absorption enhancers known to a person skilled in
the art can be used in a composition according to embodiments of the present invention. A formulation that provides an improved absorption of CGP is preferred, for example, when it is desirable to provide an immediate and high level of CGP into the respiratory system, such as when the formulation is used for treatment during an episode or an attack. In one embodiment, a method according to embodiments of the invention comprises administering to the respiratory system of the subject a formulation that provides an improved absorption of CGP into the airway.

[0053] The composition according to embodiments of the present invention can be formulated in various forms that are suitable for oral or nasal administration in view of the known technologies in the art. For example, a form of spray or expiration adapted format including microparticles, such as dry powder, can be used for intra-airway administration or transairway absorption. Dry powder may be manufactured by means of one selected from the group consisting of a bowl mill, a bead mill, a jet mill, an ultimizer, a mortar, a stonemill, spray drying and supercritical fluid. The aerodynamic average particle size of the dry powder may be optimized for administration, e.g., to allow the powder to float freely in an airstream, settle and adhere to exposed mucosal cell membranes. For airway administration, it is desirable that the aerodynamic average particle size of dry powder is typically about 0.01 to about 50 µm, preferably, about 0.1 to about 30 µm, still preferably about 0.1 to about 10 µm, in diameter. For pulmonary administration, in view of the delivery into the alveoli pulmonis, those particles having an aerodynamic average particle size of about 3 µm or less are preferably manufactured, but the present invention is not limited thereto. The powders can be inhaled or inspired. They can be dispensed via a "puff" container of any sort, including those which dispense unmetered or metered amounts.

[0054] A composition according to an embodiment of the present invention can be associated with an aerosol system, such as an aerosol spray can. The aerosol system includes, for example, vessels with propellant included therein. The propellant comprises the active ingredient CGP and conventional additives such as lactose. The formulation of the propellant determines the properties of the output of the aerosol system, such as particle distribution, delivery rate, viscosity and the like. Such aerosol systems can be manufactured using methods known in the art in view of the present disclosure.

[0055] A composition according to an embodiment of the present invention can also be an aqueous solution/suspension, which is suitable for nasal cavity administration or for inhalation, such as by direct nasal lavage, liquid stream or spray. The solution is atomized to very small particles of a size range of 1-10 µm. An aerosol finely distributed within an atomized solution can also be inhaled. Detailed information relating to aerosol inhalants is available, for example, from a
pharmacopoeia, such as the Japanese Pharmacopoeia, US Pharmacopoeia and the like, which are herein incorporated hereby as references in their entirety. The aqueous solution/suspension can be sprayed under hand-operated actuation, such as in a squeeza ble bottle or plunger, or it can be in a pressurized container.

[0056] A composition according to an embodiment of the present invention can further be a gel or cream for nasal application, in which case the ingredients would have, in addition to those described above, suitable stabilizing substances to raise the viscosity to desired levels. Examples of such stabilizing substances include, but are not limited to, sodium carboxymethyl cellulose gum (CMC gum), guar gum, xanthan gum, etc. A composition according to an embodiment of the present invention can further comprise fatty acids of vegetable source or of animal source, such as butyric acid.

[0057] In a particular embodiment of the present invention, the composition is an aqueous solution/suspension comprising about 1-5% (w/w) CGP; one or more acceptable moisturizers, such as glycerol, sorbitol and/or the like; one or more acceptable bacteriostats/mycostats, such as methyl paraben, grapefruit seed extract or the like; one or more flavorings or aromatics, such as vanilla, eucalyptis or the like, and purified, sterile water. Such a composition is applied to the respiratory system by direct nasal lavage or nasal or oral inhalation.

[0058] In another particular embodiment of the present invention, the composition is an aqueous solution/suspension comprising about 6-10% (w/w) CGP; one or more acceptable moisturizers, such as glycerol, sorbitol and/or the like; one or more acceptable bacteriostats/mycostats, such as methyl paraben, grapefruit seed extract or the like; one or more flavorings or aromatics, such as vanilla, eucalyptis or the like; purified, sterile water; a stabilizing or thickening agent; and an adhesion molecule. Such a composition is applied to the nasal cavity as a nose drop.

[0059] In another aspect, the present invention provides a device for treating or preventing a disease, disorder and/or condition of the respiratory system in a subject. The device comprises an effective amount of calcium glycerophosphate and a means for administering the effective amount of calcium glycerophosphate to the respiratory system of a subject. It should be understood that such a device may be in any format as long as the device is for facilitating the administration of calcium glycerophosphate to the respiratory system. The means for administration to the respiratory system comprises means selected from the group consisting of means for administration to the lung, means for transairway administration, means for transairway absorption and means for nasal absorption.
Exemplary means for administration to the airway include, but are not limited to, an inhaler, a respirator, a transpirator, an atomizer (e.g., a means to apply a spray/mist from a container such as a squeezed bottle or pressure container), a vaporizer, an air mask, an insufflator, and a means for direct physical or mechanical application. In particular embodiments, the means for administration to the airway is a metered dose inhaler (MDI), a dry powder inhaler (DPI), a nebulizer, a means for performing direct nasal lavage, a cotton swab, etc.

Exemplary means for administration to the lung include, but are not limited to, an inhaler and a bronchoscope, including those bronchoscope systems commercially available from Olympus Inc.

Example 1

Effectiveness of Calcium Glycerophosphate in Sensitized Brown-Norway Rats

Animal models of asthma can be used to demonstrate the effectiveness of CGP on asthma. The Brown-Norway (BN) rat model of airway hyperresponsiveness (AHR) has been shown to possess features similar to human allergic asthma, such as early- and late-phase reactions after allergen challenge and the development of an IgE response to allergic sensitization (Haczku et al., Immunology. 85(4):598-603 (1995)). Such BN AHR rats can be produced by sensitization and exposure to ovalbumin (OVA) following a method similar to that described in Eur J Pharmacol. 7:293(4):401-12 (1995) or Haczku et al. (1995), above. CGP can be administered to the BN AHR rat prior to or after irritating the BN AHR rats with OVA. The airway responsiveness can be measured prior to or after CGP administration.

Brown Norway rats (8-10 weeks old; weight: 150-300 g) are bred and maintained by adhering to standards/guidelines established by the Association for Assessment and Accreditation of Laboratory Animal Care ("AAALAC")- These rats are sensitized by giving 4 mg of aluminum hydroxylate and 1 mg ovalbumin (OVA; Sigma, grade V) in one ml of pyrogen-free saline by cervical subcutaneous injection for sensitization. Bordetellapertussis vaccine containing $3 \times 10^9$ heat inactivated bacteria is used for intraperitoneal injection as an adjuvant. As a control, the same solution described above but without ovalbumin is intraperitoneally injected, thus providing a negative control. About 10-15 days after sensitization, airway irritation is induced by challenging the rats with 5-10% aerosolized OVA for 5-10 min using a nebulizer. Aerosol exposure can be accomplished by placing the rats in a plexiglass chamber connected to a nebulizer, which generates an aerosol mist pumped into the exposure chamber by the airflow supplied by a small animal ventilator set at 60 strokes/min, with a pumping volume of 10 ml.
CGP can be administered to the rats by nasal inhalation (using an aerosol or a powder), or intubation (liquid, aerosol, respirator), either before or after the airway irritation is induced.

Airway responsiveness of the rats can be measured. Anaesthetized, tracheostomized and ventilated rats are monitored for their airflow, transpulmonary pressure and blood pressure. Lung resistance is simultaneously calculated using known method, such as a software program (LabView, National Instruments, Austin, TX). Bronchial Alveolar Lavage (BAL) fluid is collected. BAL is performed using 5 ml of phosphate buffered saline (PBS; 137 mM NaCl, 10 mM sodium phosphate buffer pH 7.4, 2.7 mM KCl), 4 times. The total number of cells in BAL fluid can be determined using an erythrocytometer and the percentage of eosinophils in BAL fluid can be determined by differential cell counting.

An OVA challenge will elicit a statistically significant increase in infiltration of inflammatory cells mainly consisting of eosinophils in the airway. The ability of CGP to suppress the increase of eosinophils in BAL fluid in response to the OVA challenge will be measured. The effectiveness of CGP can be studied at various dosages, in various formulations, at various pH, etc., together with proper control formulations.

**Example 2**

**Effectiveness of Calcium Glycerophosphate in Allergic Rhinitis Animal Models**

Animal models of rhinitis can be used to demonstrate the effectiveness of CGP on rhinitis. Methods are known to produce animal models of rhinitis. For example, a mouse model of allergic rhinitis can be developed by local sensitization of mice with *Dermatophagoides pteronyssinus* (Kim et al., *Otolaryngol Head Neck Surg*. 2007 May;136(5):720-5); and a guinea pig model of rhinitis can be developed by bilateral intranasal sensitization of guinea pigs with the instillation of cedar pollen extracts (Mizutani et al., *Jpn J Pharmacol*. 2001 Jun;86(2):170-82).

CGP can be administered to the animal models of rhinitis via desirable means such as inhalation or spray. Symptoms of rhinitis, nasal mucosa eosinophilia, serum total IgE, cytokines, and eosinophilia in BAL fluid of the animal models are measured before or after CGP administration in order to evaluate the effectiveness of CGP.

**Example 3**

**Applications of Calcium Glycerophosphate to a Human Subject Having a Respiratory Condition**

Investigation of the effectiveness of a calcium glycerophosphate for treating or preventing a disease, disorder and/or condition of the respiratory system has now been extended further to the human body.
CGP was incorporated into samples of a lavage or a spray product at varying concentrations, along with different sweetening/moisturizing components (sorbitol, glycerin) at varying levels (0.5% to 7.5% by weight), appropriate food/drug grade fungistats and bacteristats (methyl paraben and benzalkonium chloride), and light flavorings of several types (peppermint, spearmint and orange) in some iterations.

A first human subject for laboratory/home trials was a 77 year-old man in good general health. The subject has a life history of childhood asthma, which is currently inactive except for rare mild adult episodes, all of which occurred several years prior, deviated septum blocking of one nostril -60%. The subject has a history of childhood allergies to ragweed, house dust, horse hair, etc., but these are inactive at present. The subject has experienced a decades-long post nasal drip (PND) as an adult, nasal obstruction (mucus, septum). The subject has experienced coughs that have been of weeks-long and, on occasion, months-long duration, following seasonal flu or colds. The subject has experienced chronic throat-clearing from PND and chronic cough even when not post-respiratory illness, which he ascribes to bronchitis. This results in occasional inconvenience when the subject has had to excuse himself from a group to clear out throat elsewhere, including spitting out or reflexive swallowing of the mucus which will on occasion roughen voice. The subject breathed almost exclusively through mouth as a child because of nasal obstruction. The subject breathes through both nose and mouth as an adult, with breathing through nose occasionally mildly problematic, requiring active conscious engagement, although the subject was never "short of breath" in terms of lung capacity, etc.

**Forced nasal lavage experiment**

The subject performed forced nasal lavage once daily for about two weeks. The forced nasal lavage was conducted intranasally over skin and normally in a shower. An aqueous solution or suspension of CGP at various concentrations, such as about 7.5%, 3.75%, 2.5%, 2%, 1.5% by weight of dry CGP, was forced into one nostril and out of the other nostril using a closed plastic bottle with an internal stem feed. This procedure was repeated for each side of the nostrils. Some product was swallowed via nasal route and there was approx. 2 oz. fluid per nostril.

Within about 0-10 minutes after the lavage, the subject experienced considerable drainage fore and aft the nasal passages, considerable throat-clearing, and very wet nasal passages. The subject spit out some swallowing. Within about 10-20 minutes after the lavage, the subject experienced 90% decreased drainage, open and drying nasal passages, and easier breathing. Within about 20-60 minutes after the lavage, the subject felt that nasal passages remained open and drying, voice was clearer and throat-clearing was about 90% diminished compared with prior state.
about 1 hr to 12/24 hr after the lavage, the subject experienced no drip, no cough, and easy open breathing. He could breath naturally through his mouth and nose without active conscious engagement. His lower airway passages opened fully.

[0075] **Spray/mist experiments**

5 [0076] The subject applied CGP into his nostrils in a spray or a mist. A closed small plastic bottle with internal stem feed constructed to deliver fluid contents as mist was used. Typically, one application was performed in the morning. Each application consisted of two sprays per nostril, alternating sides, with full simultaneous deep breath inhalation or inspiration to draw the product up the nose and into the airway passages. The spray was also, on occasion, applied directly through the mouth to the throat with 1 or 2 sprays per application. An average spray delivery contained about 200 mg of a formulation of CGP per squeeze. The formulation contained about 2% to about 3.75% by weight of dry CGP.

10 [0077] The subject experienced benefits from the nasal spray essentially the same as those of lavage but without all the preliminary hydraulics and recovery from same. CGP exerted its relieving effects almost instantaneously upon application and the benefits lasted about four to eight hours post application. The spray/mist application was repeated occasionally in the afternoon or as needed. It was observed that a single spray per nostril at bedtime appeared to produce better night breathing. The spray/mist application was much neater, easier to operate, more portable, and more feasible for regular use.

15 [0078] After administration of the CGP to the respiratory system, either via forced nasal lavage or spray/mist, the subject experienced about 95-98% reduction of post nasal drip, a daily nuisance to subject whether upright and active or reclining, complete cessation of coughing, open breathing through his nose without any, or at worst, with minimal restriction.

[0079] In addition to the routine application of CGP to prevent or control symptoms associated with the respiratory system, the subject has also used CGP to relieve symptoms during an episode of a condition of airway/upper respiratory tract. In one morning, during early product trials, after the subject discontinued use of CGP for about 24 hours, the subject appeared to exhibit the following symptoms associated with airway/upper respiratory tract: nasal congestion, throat irritation with post-nasal drip, hoarseness, and throat clearing, faint breathing sounds, and slightly short of breath.

20 Although the symptoms did not amount to an asthma attack, the subject experienced significant discomfort. At about 10:45 A.M., the subject applied a double-dose of NasoCell (1.75% CGP by weight) via nasal inhalation in each nostril. At about 11:30 AM, the subject’s symptoms were much improved. The subject then self-administered another dose of NasoCell in each nostril. At about
12:50 P.M., it appeared that the subject's symptoms had almost completely resolved. The subject had no trouble breathing while he was eating during lunch. At about 2:30 PM, the subject's symptoms were completely resolved. The subject's throat was cleared of any obstructions and breathing sounds, and was wide open. The subject's nasal passages were reopened and voice cleared from an earlier morning huskiness, characteristic of a post nasal drip condition. It is noteworthy that this subject observed that after some weeks of usage, much reduced usage was required to "maintain", and that this included the skipping of usage altogether, some days.

Example 4

Applications of Calcium Glycerophosphate to a Human Subject Having Asthma

[0080] This Example describes a study of the effectiveness of calcium glycerophosphate to treat or prevent asthma in a human subject. A CGP composition similar to that described in Example 3, containing about 2% (w/w) CGP, was used in this study. A second human subject, a man of 44 years of age having a life history of asthma, participated in this study.

[0081] The subject intentionally stopped using Advair Diskus (steroid) for about 2 weeks. His allergies to molds were triggered by a 'musty' indoor environment resulting from several rainy and humid days. The allergies in turn triggered his asthma. The subject had felt a slight reduction in his airflow capacity for a few days, but had withheld use of albuterol inhaler (asthma rescue medication) during the day and only used it for severe wake-ups during the night. The subject had to use albuterol inhaler for three contiguous nights prior to the night described below.

[0082] In that night, at about 8:30 PM, the subject was experiencing difficulty breathing and wheezing, which signaled the start of an asthma attack. At about 8:35 PM, the subject applied two sprays of the CGP composition into each nostril and one spray of the CGP composition into his mouth for inhalation. An average spray delivery contained about 200 mg of the composition. At about 8:40 PM, the subject repeated the oral inhalation once, and the subject experienced mild relief to the extent that he did not feel the urgent need to use the albuterol inhaler. At about 8:52 PM, the subject did two additional oral inhalations of the composition. At about 8:55 PM, the subject noticed that his wheeze and tightness in chest were relieved about 80% or more. All nasal drips had been sniffed back in. At about 8:58 PM, the subject perceived a gradual improvement and experienced no labor in breathing. At about 9:05 PM, the subject felt better, but desired full relief and wanted to increase breathing capacity. He applied one inhalation of the composition into each nostril; paused to get full breath, then applied two deep oral inhalations of the composition at about 9:07 PM. At about 9:27 PM, the subject felt fine and substantially back to normal. At about 9:37 PM, the subject felt improved. At about 10:16 PM, the subject felt fully (100%) recovered. At
about 11:00 PM, the subject felt fine, no worry, and went to bed. The subject experienced no wake-up with shortness of breath and did not use inhaler during the night. At about 8:00 AM the next day, the subject felt a little tightness in chest. Instead of using 2 puffs of albuterol to start the day as he normally did, the subject used the CGP composition. He applied two sprays of the composition into each nostril and two sprays of the composition into his mouth for inhalation. He felt relief and no need to use the albuterol inhaler.

[0083] It will be appreciated by those skilled in the art that changes could be made to the embodiments described above without departing from the broad inventive concept thereof. It is understood, therefore, that this invention is not limited to the particular embodiments disclosed, but it is intended to cover modifications within the spirit and scope of the present invention as defined by the appended claims.
CLAIMS

I/we claim:

1. A method of treating or preventing a disease, disorder and/or condition of a respiratory system in a subject, the method comprising administering to the respiratory system of the subject an effective amount of calcium glycerophosphate, wherein the calcium glycerophosphate is administered to the respiratory system of the subject in a composition formulated for oral or nasal administration.

2. The method of claim 1, wherein the disease, disorder and/or condition of a respiratory system is related to an obstructive or a restrictive condition of the respiratory airway.

3. The method of claim 1, wherein the disease, disorder and/or condition of a respiratory system is a respiratory airway inflammatory disease, a respiratory airway stenosis or a nasal cavity inflammatory disease.

4. The method of claim 1, wherein the disease, disorder and/or condition of the respiratory system is selected from the group consisting of an asthma, a chronic obstructive pulmonary disease (COPD), an emphysema, a reactive airway disease (RADS), rhinitis, bronchitis, bronchiolitis, congestion, sinusitis, tonsillitis, or laryngitis, post-nasal drip (PND) and a related complication thereof, inflamed degranulating and non-degranulating mast cell activity, any irritation occasioning mucus secretion from goblet cells breathing difficulty, restriction, obstruction; airway constriction or closure or mucus interference with air passage; sleep apnea, snoring, inflammatory or non-inflammatory responses to an airborne or non-airborne allergen or irritant; nasal or non-nasal airway inflammation or irritation caused by a problem in any area of the body, a physical damage to the respiratory system, and a respiratory disease, disorder and/or condition caused by an airborne or seasonal allergen or irritant.

5. The method of claim 4, wherein the asthma is selected from the group consisting of bronchial asthma, infantile asthma, allergic asthma, atopic asthma, steroid refractory asthma, non-allergic asthma, endogenous asthma, exogenous asthma, aspirin asthma, cardiac asthma, exercise-induced asthma and infectious asthma.

6. The method of claim 4, wherein the rhinitis is selected from the group consisting of allergic rhinitis, pollinosis, acute rhinitis, chronic rhinitis, hypertrophic rhinitis, and deflected septum.

7. The method of claim 4, wherein the physical damage is nosebleed, surgery healing, or traumatic injury.
8. The method of claim 1, wherein the calcium glycerophosphate is administered in a formulation of a powder, gel, microsphere, or suspension, and the formulation provides an extended release of calcium glycerophosphate into the airway of the subject, wherein the extended release results from a higher than soluble amount of the calcium glycerophosphate in a local environment of the respiratory system.

9. The method of claim 1, wherein the calcium glycerophosphate is administered in a formulation that provides an improved absorption of calcium glycerophosphate into the airway of the subject.

10. The method of claim 1, wherein the calcium glycerophosphate is administered to the respiratory system of the subject by a nasal drop, a nasal spray, a nasal lavage, a quick-dissolving tablet, an inhaled powder, an oral inhalation solution or suspension, a syrup, a mechanized intermittent fluid pulser, an inhaler, a respirator, a transpirator, an atomizer, a vaporizer, an air mask, a means for direct physical or mechanical application, or an insufflator.

11. The method of claim 1, wherein the calcium glycerophosphate is administered to the respiratory system of the subject using a metered dose inhaler (MDI), a dry powder inhaler (DPI), a nebulizer, or a cotton swab.

12. The method of claim 1, further comprising administering to the respiratory system of the subject one or more medications for a disease, disorder and/or condition of the respiratory system.

13. The method of claim 12, wherein the one or more medications are selected from the group consisting of a beta-2 agonist, an alpha agonist, a bronchodilator, a glucocorticoid, a leukotriene modifier, a mast cell stabilizer, an antimuscarinic/anticholinergic, a methylxanthine, an antihistamine, omalizumab, methotrexate, tianeptine, albuterol, and cromolyn.

14. The method of claim 1, further comprising administering to the respiratory system of the subject an analgesic.

15. The method of claim 14, wherein the disease, disorder and/or condition of a respiratory system is a cold, a hayfever, or a respiratory disease, disorder and/or condition caused by an airborne or seasonal allergen or irritant.

16. The method of claim 14, wherein the pharmaceutical composition is formulated for nasal administration and is nasally administered to the subject.

17. The method of claim 14, wherein the analgesic is selected from the group consisting of ibuprofen, acetaminophen, aspirin, naproxen, and capsaicin.
18. The method of claim 1, wherein the subject is a human subject selected from the group consisting of a pediatric patient, an elderly patient, a pregnant woman, and a patient who has frequent need of a relief agent and/or preventive agent for the disease, disorder and/or condition of the respiratory system.

19. A composition for treating or preventing a disease, disorder and/or condition of a respiratory system in a subject, the composition comprising an effective amount of calcium glycerophosphate, wherein the composition is formulated for oral or nasal administration to the respiratory system of the subject by a nasal drop, a nasal spray, a nasal lavage, a quick-dissolving tablet, an inhaled powder, an oral inhalation solution or suspension, a syrup, a mechanized intermittent fluid pulser, an inhaler, a respirator, a transpirator, an atomizer, a vaporizer, an air mask, an insufflator, a nebulizer, or a means for direct physical or mechanical application.

20. The composition of claim 19, wherein the composition comprises a formulation selected from the group consisting of:

   (a) a formulation of a powder, gel, microsphere, or suspension;

   (b) a formulation comprising an adhesion molecule or material that allows the composition to adhere to an airway tissue for an extended period of time; and

   (c) a formulation of a powder, gel, microsphere, or suspension comprising the adhesion molecule or material.

21. The composition of claim 19, wherein the composition comprises an absorption enhancer that improves absorption of calcium glycerophosphate into an airway tissue.

22. The composition of claim 19, wherein the effective amount of calcium glycerophosphate is about 0.05% - 10% (w/w) in the composition.

23. The composition of claim 19 being formulated for administration via a metered dose inhaler (MDI), a dry powder inhaler (DPI), or a cotton swab.

24. The composition of claim 19 having a pH of about 4.5 to about 10.0.

25. The composition of claim 19 having a pH of about 4.5 to about 6.0.

26. The composition of claim 19, further comprising one or more medications selected from the group consisting of a beta-2 agonist, an alpha agonist, a bronchodilator, a glucocorticoid, a leukotriene modifier, a mast cell stabilizer, an antimuscarinic/anticholinergic, a methylxanthine, an
antihistamine, omalizumab, methotrexate, tianeptine, albuterol, cromolyn, ibuprofen, acetaminophen, aspirin and naproxen.

27. A device for treating or preventing a disease, disorder and/or condition of a respiratory system in a subject, the device comprising an effective amount of calcium glycerophosphate and a means for administering the effective amount of calcium glycerophosphate to the respiratory system of a subject.

28. The device of claim 27, wherein the means for administration to the respiratory system comprises means selected from the group consisting of means for administration to the lung, means for transairway administration, means for transairway absorption and means for nasal absorption.

29. The device according to claim 27, wherein said means for administration to the airway comprises one selected from the group consisting of an inhaler, a respirator, a transpirator, an atomizer, a vaporizer, an air mask, and an insufflator, and a means for direct physical or mechanical application.

30. The device according to claim 27, wherein said means for administration to the airway comprises one selected from the group consisting of a metered dose inhaler (MDI), a dry powder inhaler (DPI), a nebulizer, a means for nasal lavage application, and a cotton swab.
### INTERNATIONAL SEARCH REPORT

#### A CLASSIFICATION OF SUBJECT MATTER

IPCG(8) - C01 C 1/02 (2008.04)

USPC - 423/357

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)

USPC - 423/357

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

USPC - 423/357, 441, 555, 514/5

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

PubWEST/USPT, PGPB, EPAB, JPAB, Google Patents, Google

Terms Used: calcium glycerophosphate treat treatment respiratory system oral nasal administration powder gel asthma rhinitis active ingredient inhaler nebulizer analgesic allergen allergy pH modifier

#### C DOCUMENTS CONSIDERED TO BE RELEVANT

<table>
<thead>
<tr>
<th>Category</th>
<th>Citation of document, with indication, where appropriate, of the relevant passages</th>
<th>Relevant to claim No</th>
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<tr>
<td>Y</td>
<td>US 2004/01 9741 1 A1 (GAO et al) 7 October 2004 (07 10 2004) entire document especially paras [0026], [0027], [0032], [0058], [0059], [0062]</td>
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<td>Y</td>
<td>US 6,703,044 B1 (PINHASI et al) 9 March 2004 (09 03 2004), col 3, in 40-60, col 4, in 61-65</td>
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#### D Further documents are listed in the continuation of Box C

- "A" document defining the general state of the art which is not considered to be of particular relevance
- "E" earlier application or patent but published on or after the international filing date
- "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- "O" document referring to an oral disclosure, use, exhibition or other means
- "P" document published prior to the international filing date but later than the priority date claimed

- "T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- "X" document of particular relevance, the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- "Y" document of particular relevance, the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
- "&" document member of the same patent family

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<th>Date of the actual completion of the international search</th>
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