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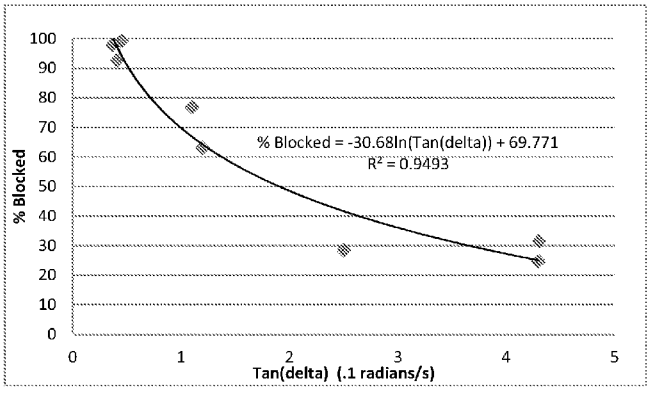


FIG. 1

(57) Abstract: A method of blocking or trapping allergens or allergen particles in the nasal cavity of a subject, comprising the steps of applying to the nasal cavity of the subject a nasal composition comprising microcrystalline cellulose; and sodium carboxymethyl-cellulose and its salt derivatives thereof, wherein the microcrystalline cellulose to sodium carboxymethylcellulose are present in a ratio of about 50:50 to about 99: 1, respectively, and wherein the nasal composition is substantially free of active pharmaceutical ingredients.

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# A METHOD OF BLOCKING OR TRAPPING ALLERGENS

## BACKGROUND OF THE INVENTION

### Field of the Invention

**[0001]** The present invention relates to nasal compositions. More particularly, the present invention relates to a method of blocking or trapping allergens using a nasal composition.

### Related Background Art

**[0002]** Allergens are non-parasitic antigens which are capable of stimulating a type-I hypersensitivity reaction in atopic individuals. Dust, pollen, dust mite and pet dander are all common airborne allergens, which have various particle sizes (5-75microns) and charges. The incidence of allergic diseases is steadily rising, but the exact reasons for this increase are unknown. A significant proportion of these patients suffer from allergic rhinitis. The disease can be described as an inflammatory response that occurs mainly in the mucous membranes of susceptible individuals after contact with trigger allergens. This response is characterized by symptoms such as sneezing; itching of the nose, throat, eyes, and ears; rhinorrhea; lacrimation; nasal congestion; and swelling of the eyes.

**[0003]** One of the main areas of entry for allergens is the nose, where the allergens interact and cause a response with nasal mucosal membrane. The nasal cavity in the nose has a nasal mucosal membrane that is covered by a thin layer of mucus. The nasal mucus is about 5-10 microns in thickness and has a high turnover rate per day with a flow rate of 8-100 mm/min in the main nasal cavity. This mucus layer acts as a barrier to stop allergens from entering

the body and is produced by goblet cell as well as submucosal cells found in the airway epithelium. Some of the components of mucus are mucins, water, salt, lysozyme, albumin, Soluble IgA, and cellular debris.

**[0004]** The primary polymer component of mucus is a class of molecules called mucins. Mucins are a family of glycoprotein and are 3-25 MDa in size. When hydrated these negatively charged, highly hydrophilic macromoleculars create a hydrogel and a thixotropic fluid. The rheology of mucus varies greatly depending on the amount of water that is available, which alters the residence time in the nasal cavity. For example, less viscous or more hydrated mucus will flow freely with gravity altering the residence time. It will also alter the barrier properties of the mucus layer.

**[0005]** The two types of allergic rhinitis, seasonal and perennial, may occur alone or as a mixed form with seasonal exacerbation. The signs and symptoms vary depending on the type and seasonal occurrence of the etiological agent (e.g., tree, grass, or grain pollen). Geographic location also plays a role in the intensity and duration of exposure to seasonal airborne allergens. Perennial allergic rhinitis is a chronic disease that is caused by exposure to and contact with nonseasonal allergens that are found, for example, in animals and house dust. Perennial allergic rhinitis produces symptoms similar to those of seasonal allergic rhinitis, but nasal congestion is the chief complaint, and conjunctivitis is less common.

**[0006]** Type I allergies are commonly treated by corticosteroids, anti-histamines and mast cell stabilizers. These drugs are anti-inflammatory, or block the action of allergic mediators by preventing activation of cells or degranulation processes. All these therapeutics help to alleviate the symptoms of allergy but, especially after long-term and high-dose medication, they can have quite substantial side-effects. In particular, oral corticosteroids can cause general immuno-suppression, skin fragility and Cushing's syndrome, and even new

generation anti-histamines are not completely void of sedative effects. Therefore, there is still a vital need for the development of new anti-allergic drugs with satisfactory tolerability for long-term use. They should be effective on the early as well as the late phase allergic reactions. Treatment strategies like allergen avoidance or desensitization play an important role to achieve a long-term improvement of symptoms. The methods for allergen avoidance vary and may include mechanical measures such as air filters and masks for pollen reduction and/or ointments/sprays to form a barrier in the nose region to entrap allergens. These measures will reduce the number of allergens entering the nose (e.g., pollen, house dust, animal dander) thereby relieving allergy symptoms.

**[0007]** Recently, products have been proposed for blocking allergens by creating an electrostatic barrier before they enter the nasal cavity, including the use of petrolatum based compositions that are intended for application on the upper lip or below the nostril. These products do not have a uniform product placement and are not discrete to the individual.

**[0008]** Viscous topical nasal creams are also available, which consist of highly refined aliphatic long-chain hydrocarbons for prophylaxis and therapy of allergic rhinitis caused by airborne allergens.

**[0009]** These creams are applied by finger or cotton swab to the inside surface of the nasal vestibule in the region of the nose flap where it acts as a mechanical barrier to reduce the adverse effects of inhaled allergens.

**[0010]** The hydrocarbon gel is chemically inert to the body and nasal membranes and contains no additives. It does not penetrate the skin and is not absorbed.

## SUMMARY OF THE INVENTION

**[0011]** The present invention is directed to a method of blocking or trapping allergens or allergen particles in the nasal cavity of a subject, comprising the steps of applying to the nasal cavity of the subject a nasal composition comprising microcrystalline cellulose; and sodium carboxymethylcellulose and its salt derivatives thereof, wherein the microcrystalline cellulose to sodium carboxymethylcellulose are present in a ratio of about 50:50 to about 99:1, respectively, and wherein the nasal composition is substantially free of active pharmaceutical ingredients.

## BRIEF DESCRIPTION OF THE DRAWINGS

**[0012]** FIG. 1 is a graph showing the relationship of the Blocking Percentage versus Tan(delta);

**[0013]** FIG. 2 is a graph showing the relationship of the Blocking Percentage versus Complex Viscosity; and

**[0014]** FIG. 3 is a model representation of a nasal cavity.

## DETAILED DESCRIPTION OF THE INVENTION

**[0015]** As used herein, "substantially free" is understood to mean that a component is present at a level or in an amount which does not elucidate a therapeutic response. In one embodiment, the composition of the present invention is substantially free of a pharmaceutical active ingredient. In another embodiment, the composition is substantially free of an upper respiratory active ingredient at a level defined as minimally efficacious by

the United States Food and Drug Administration monograph. In yet another embodiment, the composition is substantially free of one or more upper respiratory active pharmaceutical ingredients from the group consisting of antihistamines, decongestants, or nasal steroids. In still yet another embodiment, the composition is substantially free of menthol, e.g., less than about 0.01% menthol. Alternatively, for components that do not function to provide a therapeutic response, substantially free is understood to mean at a level less than 1% by weight, preferably, less than 0.5% by weight, and more preferably, less than 0.01% by weight.

**[0016]** As used herein, "yield stress" is understood to mean the minimum stress that must be applied to initiate significant flow and a significant drop in viscosity. That is, the applied stress must equal or exceed the threshold value to make a structured fluid flow.

**[0017]** As used herein, "stable" refers to a composition that retains the same rheological properties of viscosity and spreadability and the same barrier properties upon storage for at least about 6 months at 40°C and 75% relative humidity conditions.

**[0018]** The current invention is a method of blocking or trapping allergens or allergen particles in the nasal cavity of a subject. The method comprises the step of applying to the nasal cavity of the subject a nasal composition comprising microcrystalline cellulose, and sodium carboxymethylcellulose and its salt derivatives thereof, wherein the microcrystalline cellulose to sodium carboxymethylcellulose are present in a ratio of about 50:50 to about 99:1, respectively, and wherein the nasal composition is substantially free of active pharmaceutical ingredients.

**[0019]** The composition is used to create a barrier on the nasal mucosal surface in the inferior meatus and middle meatus of the human nasal cavity to reduce exposure of these regions to airborne allergens and/or contaminants. The thin film barrier works in conjunction with the

body's host defense, such as mucus and is a non-pharmaceutical approach to providing allergy relief.

**[0020]** When applied, the nasal composition creates/forms a thin film barrier within the nasal cavity. The barrier film is water soluble or a hydrogel.

**[0021]** The inventive method applies a composition to create a barrier on the nasal mucosal surface in the inferior meatus and middle meatus of the human nasal cavity to reduce exposure of these regions to airborne allergens and/or contaminants. The thin film barrier works in conjunction with the body's host defense, such as mucus and is a non-pharmaceutical approach to providing allergy relief.

**[0022]** The nasal composition of the present invention includes a nasal spray/gel composition comprising microcrystalline cellulose and sodium carboxymethylcellulose, (e.g., commercially available as Avicel RC-591). Moreover, the ratio (by weight) of microcrystalline cellulose to sodium carboxymethylcellulose is about 50:50 to about 99:1, respectively. The nasal composition may further include a buffering system (dibasic and monobasic sodium phosphate) and optionally, a sensate system (cool flavor and menthol). Additionally, the pH of the composition may be between about 5 and about 6. This is a shear thinning composition which thickens upon deposition in the nasal cavity, thereby providing a barrier which traps allergen particles. One of the key features of the inventive method is the use of a composition, which is substantially free of a pharmaceutical active ingredient. The composition used is intended to trap allergen particles and slow the transport (not act as an antihistamine or decongestant) of allergens to the mucosal tissue. This delay in transport means that the allergic response is not activated and the body's natural defenses such as mucocillary clearance can occur. Ideally, the composition is applied prior to exposure to potential allergen particles. However, this is not a necessary prerequisite for the method to be

effective. The composition has a viscosity such that it may be carried into a spray bottle and applies from a spray and deposited in the middle region of the nasal cavity. Trapped allergens are either swallowed or become inactive with time as they reside in the composition.

**[0023]** Essential ingredients in the inventive nasal composition are microcrystalline cellulose and sodium carboxymethylcellose (CMC). In one embodiment, the combined level of microcrystalline cellulose and sodium carboxymethylcellulose is at least 0.5% by weight (wt.%). In another embodiment, the level of microcrystalline cellulose and sodium carboxymethylcellulose are present at a combined level of about 0.5% by weight based on the total weight of the composition. In yet another embodiment, the microcrystalline cellulose and sodium carboxymethylcellulose are present in a combined amount from about 0.5 wt.% to about 10 wt.% based on the total weight of the composition. Alternatively, the microcrystalline cellulose and sodium carboxymethylcellulose may be present in a ratio (by weight) of about 50:50 to about 99:1, respectively. In one embodiment, the ratio (by weight) is about 70:30 to about 99:1. In another embodiment, the ratio (by weight) is about 85:15 to about 90:10. Mirocrystalline cellulose and sodium carboxymethylcellulose are commercially available from the FMC Corporation as AVICEL® RC-581, AVICEL® CL611 and AVICEL® RC-591. AVICEL® RC-581 and RC-591 are each composed of microcrystalline cellulose and sodium carboxymethylcellulose at a ratio (by weight) of 89:11, respectively. AVICEL® CL-611 is composed of microcrystalline cellulose to sodium carboxymethylcellulose at a ratio (by weight) of 85:15. The recommended weight percentage for Avicel RC-591 for gelling properties is around 1.5 weight percent from the manufacturer.

**[0024]** It is advantageous for the composition of the present invention to be deposited in specific regions of the nasal cavity. Excessive deposition of the nasal composition in the

olfactory region and the posterior region of the nasal cavity can lead to rapid wash away and loss in efficacy. Moreover, excessive deposition of the nasal composition in the front of the nose can lead to dripping and loss in efficacy of the composition for the intended purpose of trapping allergen particles. Therefore, it is desirable to have a majority of the nasal composition be deposited in the inferior meatus and middle meatus of the nasal cavity.

**[0025]** A broader group of polymers can also be included in the composition used to trap allergens. These include, polyvinylpyrrolidone and/or derivatives thereof, carageenan, hypromellose, hydroxypropylcellulose, polyvinyl alcohol, methacrylates, polyethylene oxide, gellan gum, acacia, alginic acid, bentonite, carbomers, carboxymethylcellulose, ethylcellulose, gelatin, hydroxyethylcellulose, magnesium aluminum silicate (Veegum®), methylcellulose, poloxamers (Pluronics®), sodium alginate, tragacanth, xanthan gum, guar gum, clays (Laponite, Hectorite), Sodium acrylate/acryloyldimethyl taurate copolymer & Isohexadecane & Polysorbate 80 (Simulgel EG), poly(ethylene oxide) polymers (Polyox), cross-linked copolymer of Vinyl Pyrrolidone (VP) and Acrylic Acid (AA) (ULTRATHIX™ P-100), synthetic high molecular weight polymers of acrylic acid (CARBOMER), fucoidan, locust bean gum, and mixtures thereof.

**[0026]** Carbomer is a generic name for a family of polymers known as Carbopol®. They are characterized by being dry powders with high bulk densities, and form acidic aqueous solutions (pH around 3.0). They thicken at pHs around 5 - 6 or higher. And they will swell, as much as 1000 times their original volume, in aqueous solution at that pH. Their solutions range in viscosity from 0 to 80,000 centipoise (cps).

**[0027]** In one preferred embodiment, the nasal composition includes polyvinylpyrrolidone and/or derivatives thereof. For purposes of the discussion herein, references to polyvinylpyrrolidone are intended to include its derivatives thereof. Polyvinylpyrrolidone is

known to bind to polar molecules. The polyvinylpyrrolidone can coat or bind the allergens so that they cannot cause an allergic response. It is also typically used in multiple applications, such as, for example, an emulsifier, a powder granulation binder, a thickening agent, or as an adhesive agent.

**[0028]** Derivatives of polyvinylpyrrolidone include, for example, polyvinylpolypyrrolidone, complexes of polyvinylpyrrolidone such as povidone-iodine and the like.

**[0029]** Polyvinylpyrrolidone suitable for use in the present invention preferably has an average molecular weight in the range of about 1,500 to about 3,000,000 g/mol, more preferably in the range of about 2,500 to about 500,000 g/mol. Grades of polyvinylpyrrolidone of average molecular weight 10,000 and 40,000 are available from Sigma Chemical Company, whilst a grade with an average molecular weight of 30,000 is available from GAF Corporation (e.g., povidone (Plasdone K-29/32)).

**[0030]** Polyvinylpyrrolidone is suitably present in at least about 0.5%, preferably between about 0.5% and about 30%, more preferably between about 2% and about 30%, advantageously between about 5% and about 25%, by weight of the composition.

**[0031]** Other molecules that function similarly to polyvinylpyrrolidone include polycationic copolymers of vinylpyrrolidone with vinylamine, and polyvinyl alcohol.

**[0032]** Compositions according to the invention will have a pH, which is suitably acceptable. For example, a pH in the range of about 2 to about 9.5, preferably in the range of about 4 to about 8 is suitably acceptable.

**[0033]** In one embodiment, the nasal composition has a yield stress of at least about 0.016 Pa at 25 °C when measured using a Rheometric Scientific RFSII rheometer (conditions).

**[0034]** In another embodiment, the composition has a yield stress of at least about 0.031 Pa at 25 °C using a Rheometric Scientific RFSII rheometer (conditions).

**[0035]** Yet in another embodiment, the composition has a yield stress of at least about 0.053 Pa at 25 °C using a Rheometric Scientific RFSII rheometer (conditions).

**[0036]** In another embodiment, the composition has a Tan(delta) of no more than 2.5 .1 radians/s with a more favorable barrier properties at a tan(delta) below 1.5 .1 radians/s.

**[0037]** A composition according to the invention may be used alone or simultaneously with, another nasal composition or other allergy medicine.

**[0038]** Optionally, a variety of ingredients may be included in the composition of the present invention. Optional ingredients include, for example, a sensate, buffering agent, surfactant, viscosity modifiers, polyethylene glycol, glycerin, sorbitol, preservative, coloring agent, flavor and mixtures thereof. In one embodiment, the composition is substantially free of moisturizing agents.

**[0039]** Any coloring agent suitable for use in a food or pharmaceutical product may be used in the present invention. Typical coloring agents include, for example, azo dyes, quinopthalone dyes, triphenylmethane dyes, xanthene dyes, indigoid dyes, iron oxides, iron hydroxides, titanium dioxide, natural dyes, and mixtures thereof. More specifically, suitable colorants include, but are not limited to patent blue V, acid brilliant green BS, red 2G, azorubine, ponceau 4R, amaranth, D&C red 33, D&C red 22, D&C red 26, D&C red 28, D&C yellow 10, FD&C yellow 5, FD&C yellow 6, FD&C red 3, FD&C red 40, FD&C blue 1, FD&C blue 2, FD&C green 3, brilliant black BN, carbon black, iron oxide black, iron oxide red, iron oxide yellow, titanium dioxide, riboflavin, carotenes, antyhocyanines, turmeric, cochineal extract, clorophyllin, canthaxanthin, caramel, betanin, and mixtures thereof.

**[0040]** Similarly, a sensate may be included in the nasal composition. The sensate may be, for example, a fragrance, flavor, and the like. The amount of the sensate added to the composition is dependent upon the desired characteristics.

**[0041]** In one embodiment, a sensate included in the nasal composition is a cooling flavor, such as menthol.

**[0042]** The composition may contain viscosity modifiers such as xanthan gum to develop the desired texture and consistency, preservatives such as sodium benzoate, benzyl alcohol, benzalkonium chloride, buffers such as citric acid, edetate disodium, monobasic sodium phosphate, dibasic sodium phosphate or mixtures thereof.

**[0043]** The composition of the present invention may also have a specific salt content, as the salt content may influence the final rheological properties and polymer structure in solution. In one embodiment the composition is substantially free of inorganic salts. In this embodiment, substantially free is defined as less than 0.2 percent of an inorganic salt.

**[0044]** In one embodiment the composition is substantially free of an active pharmaceutical ingredient (API). As used herein, an active pharmaceutical agent is defined as any substance or mixture of substances intended to be used in the manufacture of a drug (medicinal) product and that when used in the production of a drug becomes an active ingredient of the drug product. Such substances are intended to furnish pharmacological activity or other direct effect in the diagnosis, cure, mitigation, treatment or prevention of disease or to affect the structure and function of the body. In one embodiment the composition is substantially free of an active pharmaceutical ingredient (API) which is systemically absorbed through the nasal mucosa. As used herein, substantially free is defined at a level which may elucidate a therapeutic response. In one embodiment the composition is substantially free of an upper respiratory active ingredient at a level defined as minimally efficacious by the United States Food and

Drug Administration monograph. In one embodiment the composition is substantially free of one or more upper respiratory active pharmaceutical ingredients from the group consisting of antihistamines, decongestants, or nasal steroids. In one embodiment the composition is substantially free of menthol, e.g., less than 0.01% by weight menthol.

**[0045]** The composition of the present invention may be made by any method known to those skilled in the art so long as it results in the desired composition.

**[0046]** For example, compositions according to the invention may be prepared by conventional processes comprising mixing the ingredients together in the appropriate relative amounts in any order that is convenient and if necessary adjusting the pH to the desired value.

**[0047]** The barrier properties of the composition used in the present invention are significant in demonstrating the efficiency to which an allergy nasal composition may block allergen particles in the nasal cavity. The barrier property may be defined by the Transwell barrier test, wherein the percent diffusion of fluorescence is compared to a control by calculating the amount of a large molecule (in this case, fluorescein) which is passed through the barrier in the formulation of the present invention. The fluorescence is measured using a fluorescent plate reader after 62 minutes. In one embodiment, the percent decrease is at least about 15%. In another embodiment, the percent decrease is at least about 33%. And in still another embodiment, the percent decrease is at least about 76%. Flouroscein sodium has a molecular weight of 376.28 g/mol. In one embodiment, the composition of the present invention is effective at blocking compounds or particulates with a molecular weight of at least 376.28 g/mol.

**[0048]** In one embodiment when allergy sufferers used the product for 7 days during high pollen count week in August, over 65% liked the product and reported that it helped reduce

allergy symptoms, helped prevent allergy symptoms, was effective in managing allergies, had a long lasting effect and came in a form they like.

**[0049]** In another embodiment, when allergy sufferers used the product for 7 days during high pollen count in May, over 80% liked the product and reported that the product started to work quickly, lasted for stated duration of 4-6 hours on the package, product helped reduce allergy symptoms, helped prevent allergy symptoms and was effective in managing allergies.

**[0050]** In one embodiment, the nasal of the present composition is a liquid prior to dispensing, wherein all the ingredients are all in a suspension or a solution.

**[0051]** In another embodiment, the nasal composition is a gel after dispensing.

**[0052]** In one embodiment, no particles greater than 1 micron are dispersed in the liquid of the present composition.

**[0053]** The nasal composition may be applied using various means, for example, the composition may be applied using a pump, finger, swab or tube.

**[0054]** Preferably, the composition is applied to the inferior meatus and middle meatus of the nasal cavity. In one embodiment, at least 30% by weight of the composition is applied to the inferior meatus and middle meatus of the nasal cavity using an in vitro nasal model. Preferably, at least 50% by weight of the composition is applied to these desirable regions.

**[0055]** The composition is effective and/or capable of blocking allergens for at least about one hour and ideally 4-6 hours. One advantage of using the composition is that it may be applied as often as needed.

**[0056]** The following examples are provided to further illustrate the compositions and methods of the present invention. It should be understood that the present invention is not limited to the examples described.

**EXAMPLE 1: COMPOSITIONS**

**LIQUID FORMULA 1 (with Avicel and PVP)**

**[0057]** The composition for the nasal spray/gel is shown in Table 1. Approximately 75% (by weight) of the purified water was added to a suitable stainless steel container, and the microcrystalline cellulose and carboxymethylcellulose (Avicel RC-591) was added while mixing using a laboratory shear mixer and mixed until completely hydrated. The Povidone USP was added to the Avicel solution while mixing using a propeller mixer, and mixed until dissolved to create the Main Mix. In a suitable glass beaker, the Edetate Disodium, Dibasic Sodium Phosphate and Monobasic Sodium Phosphate were added to approximately 25% (by weight) of the purified water while mixing with a laboratory mixer until dissolved. In another suitable glass beaker, the Polysorbate 80 NF, Polyethyelene Glycol 400 NF, Glycerin USP, Benzyl Alcohol NF, and the Flavor (including Menthol) were mixed using a laboratory mixer and applying some heat if necessary until dissolved. The two solutions from the glass beakers were added in sequence to the Main Mix while stirring until each one was dissolved.

**TABLE 1**

| Ingredient | G/Batch | Weight Percent |
|---|---|---|
| Purified Water USP | 4592.79 | 91.8558 |
| Microcrystalline Cellulose and Carboxymethylcellulose Sodium NF (Avicel RC-591)[1] | 80.00 | 1.600 |
| Povidone USP (Plasdone K-29/32)[2] | 150.00 | 3.000 |
| Edetate Disodium USP (Dihydrate) | 15.00 | 0.300 |
| Dibasic Sodium Phosphate USP (Anhydrous) | 2.635 | 0.0527 |
| Monobasic Sodium Phosphate USP (Anhydrous) | 10.00 | 0.2000 |
| Polysorbate 80 NF (Tween 80V Pharma) | 0.50 | 0.0100 |
| Polyetheylene Glycol 400 NF[3] | 50.00 | 1.000 |
| Glycerine USP | 50.00 | 1.00 |
| Benzyl Alcohol NF | 45.00 | 0.9000 |
| Flavor[4] | 3.75 | 0.0750 |
| Menthol USP | 0.325 | 0.00650 |
| Total | 5000.00 | 100.00 |

1: Commercially available from the FMC Corporation in Philadelphia, PA
2: Commercially available from International Specialty Products, Wayne, PA

3: Commercially available from Clariant PF in Rothausstr, Switzerland
4: Commercially available from International Flavors & Fragrances New York, NY

**LIQUID FORMULA 2 (with Avicel and PVP)**

**[0058]** The composition for the nasal spray/gel is shown in Table 2. Approximately 75% (by weight) of the purified water was added to a suitable stainless steel container, and the microcrystalline cellulose and carboxymethylcellulose (Avicel RC-591) was added while mixing using a laboratory shear mixer and mixed until completely hydrated. The Povidone USP was added to the Avicel solution while mixing using a propeller mixer, and mixed until dissolved to create the Main Mix. In a suitable glass beaker, the Edetate Disodium, Dibasic Sodium Phosphate, Monobasic Sodium Phosphate, Sorbitol Solution 70%, and Benzalkonium Chloride were added to approximately 25% (by weight) of the purified water while mixing with a laboratory mixer until dissolved. In another suitable glass beaker, the Polysorbate 80 NF, Polyethyelene Glycol 400 NF, Benzyl Alcohol NF, and the Flavor were mixed using a laboratory mixer and applying some heat if necessary until dissolved. The two solutions from the glass beakers were added in sequence to the Main Mix while stirring until each one was dissolved.

**TABLE 2**

| Ingredient | Weight Percent |
|---|---|
| Purified Water USP | 92.05685 |
| Microcrystalline Cellulose and Carboxymethylcellulose Sodium NF (Avicel RC-591)[1] | 1.600 |
| Povidone USP (Plasdone K-29/32)[2] | 3.000 |
| Edetate Disodium USP (Dihydrate) | 0.300 |
| Dibasic Sodium Phosphate USP (Anhydrous) | 0.0527 |
| Monobasic Sodium Phosphate USP (Anhydrous) | 0.2000 |
| Polysorbate 80 NF (Tween 80V Pharma) | 0.0100 |
| Polyetheylene Glycol 400 NF[3] | 1.000 |
| Sorbitol Solution 70% | 0.714 |
| Benzyl Alcohol NF | 0.9000 |
| Flavor[4] | 0.07825 |
| Benzalkonium Chloride 17% Solution* | 0.0882 |

| | |
|---|---|
| Total | 100.00 |

1: Commercially available from the FMC Corporation in Philadelphia, PA
2: Commercially available from International Specialty Products, Wayne, PA
3: Commercially available from Clariant PF in Rothausstr, Switzerland
4: Commercially available from International Flavors & Fragrances New York, N005 c9
* equivalent to 0.015% w/w Benzalkonium Chloride

**LIQUID FORMULA 3 (with Avicel)**

**[0059]** The composition for the nasal spray/gel is shown in Table 3. Approximately 75% (by weight) of the purified water was added to a suitable stainless steel container, and the microcrystalline cellulose and carboxymethylcellulose (Avicel RC-591) was added while mixing using a laboratory shear mixer and mixed until completely hydrated to create the Main Mix. In a suitable glass beaker, the Edetate Disodium, Dibasic Sodium Phosphate, Monobasic Sodium Phosphate, Sorbitol Solution 70%, and Benzalkonium Chloride were added to approximately 25% (by weight) of the purified water while mixing with a laboratory mixer until dissolved. In another suitable glass beaker, the Polysorbate 80 NF, Polyethyelene Glycol 400 NF, Benzyl Alcohol NF, and the Flavor were mixed using a laboratory mixer and applying some heat if necessary until dissolved. The two solutions from the glass beakers were added in sequence to the Main Mix while stirring until each one was dissolved.

**TABLE 3**

| Ingredient | Weight Percent |
|---|---|
| Purified Water USP | 95.05685 |
| Microcrystalline Cellulose and Carboxymethylcellulose Sodium NF (Avicel RC-591)[1] | 1.600 |
| Edetate Disodium USP (Dihydrate) | 0.300 |
| Dibasic Sodium Phosphate USP (Anhydrous) | 0.0527 |
| Monobasic Sodium Phosphate USP (Anhydrous) | 0.2000 |
| Polysorbate 80 NF (Tween 80V Pharma) | 0.0100 |
| Polyetheylene Glycol 400 NF[2] | 1.000 |
| Sorbitol Solution 70% | 0.714 |
| Benzyl Alcohol NF | 0.9000 |
| Flavor[3] | 0.07825 |
| Benzalkonium Chloride 17% Solution* | 0.0882 |

| | |
|---|---|
| Total | 100.00 |

1: Commercially available from the FMC Corporation in Philadelphia, PA
2: Commercially available from Clariant PF in Rothausstr, Switzerland
3: Commercially available from International Flavors & Fragrances New York, N005 c9
* equivalent to 0.015% w/w Benzalkonium Chloride

**LIQUID FORMULA 4 (Comparative – without Avicel)**

**[0060]** The composition for the nasal spray/gel is shown in Table 4. Approximately 75% (by weight) of the purified water was added to a suitable stainless steel container, and the Povidone USP was added while mixing using a laboratory shear mixer and mixed until completely hydrated to create the Main Mix. In a suitable glass beaker, the Edetate Disodium, Dibasic Sodium Phosphate, Monobasic Sodium Phosphate, Sorbitol Solution 70%, and Benzalkonium Chloride were added to approximately 25% (by weight) of the purified water while mixing with a laboratory mixer until dissolved. In another suitable glass beaker, the Polysorbate 80 NF, Polyethyelene Glycol 400 NF, Benzyl Alcohol NF, and the Flavor were mixed using a laboratory mixer and applying some heat if necessary until dissolved. The two solutions from the glass beakers were added in sequence to the Main Mix while stirring until each one was dissolved.

**TABLE 4**

| Ingredient | Weight Percent |
|---|---|
| Purified Water USP | 93.65685 |
| Povidone USP (Plasdone K-29/32)[1] | 3.000 |
| Edetate Disodium USP (Dihydrate) | 0.300 |
| Dibasic Sodium Phosphate USP (Anhydrous) | 0.0527 |
| Monobasic Sodium Phosphate USP (Anhydrous) | 0.2000 |
| Polysorbate 80 NF (Tween 80V Pharma) | 0.0100 |
| Polyetheylene Glycol 400 NF[2] | 1.000 |
| Sorbitol Solution 70% | 0.714 |
| Benzyl Alcohol NF | 0.9000 |
| Flavor[3] | 0.07825 |
| Benzalkonium Chloride 17% Solution* | 0.0882 |
| Total | 100.00 |

1: Commercially available from International Specialty Products, Wayne, PA
2: Commercially available from Clariant PF in Rothausstr, Switzerland

3: Commercially available from International Flavors & Fragrances New York, N005 c9
* equivalent to 0.015% w/w Benzalkonium Chloride

**LIQUID FORMULA 5 (Comparative – without Avicel and without PVP)**

**[0061]** The composition for the nasal spray/gel is shown in Table 5. Approximately 75% (by weight) of the purified water was added to a suitable stainless steel container to create the Main Mix. In a suitable glass beaker, the Edetate Disodium, Dibasic Sodium Phosphate, Monobasic Sodium Phosphate, Sorbitol Solution 70%, and Benzalkonium Chloride were added to approximately 25% (by weight) of the purified water while mixing with a laboratory mixer until dissolved. In another suitable glass beaker, the Polysorbate 80 NF, Polyethyelene Glycol 400 NF, Benzyl Alcohol NF, and the Flavor were mixed using a laboratory mixer and applying some heat if necessary until dissolved. The two solutions from the glass beakers were added in sequence to the Main Mix while stirring until each one was dissolved.

**TABLE 5**

| Ingredient | Weight Percent |
|---|---|
| Purified Water USP | 96.65685 |
| Edetate Disodium USP (Dihydrate) | 0.300 |
| Dibasic Sodium Phosphate USP (Anhydrous) | 0.0527 |
| Monobasic Sodium Phosphate USP (Anhydrous) | 0.2000 |
| Polysorbate 80 NF (Tween 80V Pharma) | 0.0100 |
| Polyetheylene Glycol 400 NF[1] | 1.000 |
| Sorbitol Solution 70% | 0.714 |
| Benzyl Alcohol NF | 0.9000 |
| Flavor[2] | 0.07825 |
| Benzalkonium Chloride 17% Solution* | 0.0882 |
| Total | 100.00 |

1: Commercially available from Clariant PF in Rothausstr, Switzerland
2: Commercially available from International Flavors & Fragrances New York, N005 c9
* equivalent to 0.015% w/w Benzalkonium Chloride

**LIQUID FORMULA 6 (Comparative – Hypromellose)**

**[0062]** The composition for the nasal spray/gel is shown in Table 6. Approximately 75% (by weight) of the purified water was added to a suitable stainless steel container, and the

Hypromellose was added while mixing using a laboratory shear mixer and mixed until completely hydrated. The Povidone USP was added to the Hypromellose solution while mixing using a propeller mixer, and mixed until dissolved to create the Main Mix. In a suitable glass beaker, the Edetate Disodium, Dibasic Sodium Phosphate and Monobasic Sodium Phosphate were added to approximately 25% (by weight) of the purified water while mixing with a laboratory mixer until dissolved. In another suitable glass beaker, the Polysorbate 80 NF, Polyethyelene Glycol 400 NF, Glycerin USP, Benzyl Alcohol NF, and the Flavor (including Menthol USP) were mixed using a laboratory mixer and applying some heat if necessary until dissolved. The two solutions from the glass beakers were added in sequence to the Main Mix while stirring until each one was dissolved.

**TABLE 6**

| Ingredient | Weight Percent |
|---|---|
| Purified Water USP | 95.86985 |
| Hypromellose (Methocel K4M) | 0.300 |
| Povidone USP (Plasdone K-90)[1] | 0.100 |
| Edetate Disodium USP (Dihydrate) | 0.300 |
| Dibasic Sodium Phosphate USP (Anhydrous) | 0.02065 |
| Monobasic Sodium Phosphate USP (Anhydrous) | 0.3430 |
| Polysorbate 80 NF (Tween 80V Pharma) | 0.050 |
| Polyetheylene Glycol 400 NF[2] | 1.0 |
| Glycerine USP | 1.0 |
| Benzyl Alcohol NF | 0.90 |
| Flavor[3] | 0.150 |
| Menthol USP | 0.00650 |
| Total | 100.00 |

1: Commercially available from International Specialty Products, Wayne, PA
2: Commercially available from Clariant PF in Rothausstr, Switzerland
3: Commercially available from International Flavors & Frangrances New York, NY

**LIQUID FORMULA 7 (Comparative – with Carrageenan)**

**[0063]** The composition for the nasal spray/gel is shown in Table 7. Approximately 75% (by weight) of the purified water was added to a suitable stainless steel container, and the Carrageenan NF was added while mixing using a laboratory shear mixer and mixed until

completely hydrated to create the Main Mix. In a suitable glass beaker, the Edetate Disodium, Dibasic Sodium Phosphate and Monobasic Sodium Phosphate were added to approximately 25% (by weight) of the purified water while mixing with a laboratory mixer until dissolved. In another suitable glass beaker, the Polysorbate 80 NF, Polyethyelene Glycol 400 NF, Glycerin USP, Benzyl Alcohol NF, and the Flavor (including Menthol USP) were mixed using a laboratory mixer and applying some heat if necessary until dissolved. The two solutions from the glass beakers were added in sequence to the Main Mix while stirring until each one was dissolved.

**TABLE 7**

| Ingredient | G/Batch | Weight Percent |
|---|---|---|
| Purified Water USP | 4800.25 | 96.01 |
| Carrageenan NF(Gelcarin GP-379)[1] | 12.50 | 0.250 |
| Edetate Disodium USP (Dihydrate) | 15.00 | 0.300 |
| Dibasic Sodium Phosphate USP (Anhydrous) | 5.53 | 0.1106 |
| Monobasic Sodium Phosphate USP (Anhydrous) | 17.15 | 0.3430 |
| Polysorbate 80 NF (Tween 80V Pharma) | 0.50 | 0.0100 |
| Polyethylene Glycol 400 NF[3] | 50.00 | 1.000 |
| Glycerin USP 70%[4] | 50.00 | 1.000 |
| Benzyl Alcohol NF | 45.00 | 0.900 |
| Flavor[4] | 3.75 | 0.0750 |
| Menthol (L) USP | 0.325 | 0.0065 |
| Total | 5000.00 | 100.00 |

1: Commercially available from FMC Biopolymer in Philadelphia PA
2: Commercially available from International Specialty Products, Wayne, PA
3: Commercially available from Clariant PF in Rothausstr, Switzerland
4: Commercially available from International Flavors & Fragrances New York, NY

**POWDER FORMULA 8 (Comparative – Hypromellose)**

**TABLE 8**

| **Ingredient** | **Weight Percent (w/w)** |
|---|---|
| Hypromellose (Methocel E15 Premium LV) | 98.0 |
| Fragrance | 2.00 |

**POWDER FORMULA 9 (Comparative – with Carboxymethylcellulose Sodium NF)**

**TABLE 9**

| Ingredient | Weight Percent (w/w) |
|---|---|
| Carboxymethylcellulose Sodium 7LXF PH | 98.0 |
| Fragrance | 2.00 |

**EXAMPLE 2: FLUORESCENT PLATE/TRANSWELL DATA**

**[0064]** Method: Utilizing Costar ® Transwell® plates (3415, 24 well plates with 6.5 mm diameter inserts and 3.0 micometer pore size, Tissue Culture Treated, Polycarbonate membranes, Sterile, Polystyrene Plates Corning incorporated) to create a vertical diffusion model. The transwell plates, have an insert that creates a separate upper chamber which is separated by the lower/bottom well by a porous membrane. The 75 microliters of the specific formulation is placed in the transwell and a fluorescent dye (Fluorescein (sodium salt) water soluble, powder, grade 41% min., EMD Chemicals, Item # FX0325-5) ( 0.018 g in 1 mL sterile water) is placed in the upper chamber with an additional 75 microliters of water. The diffusion through the membrane is monitored with a fluorescent plate reader (Spectra MaxGeminiEm, Molecular Devices). Settings: Bottom Read, Excitation: 494nm, Emission: 521nm, Cutoff filter: 515nm and below. After 62 minutes after the dye was added the transwell was removed. The fluorescence in the bottom well is measured with the fluorescent plate reader. The data shown in Tables 10 and 11 show that the combination of microcrystalline cellulose and sodium carboxymethylcellulose blocks the most fluoscein form diffusing from the top well to the bottom well. The two polymers together show an added benefit when compared to the formulations which only used one of the polymers.

**TABLE 10: Average Fluorescent Intensity (N=3)**

| | Formula 2 | with Avicel | without Avicel | without Avicel & without PVP | HPMC | Carrageenan | Transwell Control | Dye Control |
|---|---|---|---|---|---|---|---|---|
| Formula | 2 | 3 | 4 | 5 | 6 | 7 | | |
| Plate 1 | 13736 | 32411 | 135516 | 182945 | 132481 | 133136 | 201003 | 204146 |
| Plate 2 | 13831 | 35897 | 134180 | 153656 | 123778 | 135230 | 189299 | 205728 |

*Avicel is the tradename for Microcrystalline cellulose and sodium carboxymethylcellulose

**TABLE 11: Percent Decrease Of Fluorescent Intensity Formulation Compared To Transwell Control Average**

| | Formula 2 | with Avicel | without Avicel | without Avicel & without PVP | HPMC | Carrageenan |
|---|---|---|---|---|---|---|
| Formula | 2 | 3 | 4 | 5 | 6 | 7 |
| Plate 1 | 93% | 84% | 33% | 9.00% | 34% | 34% |
| Plate 2 | 93% | 81% | 29% | 18.80% | 35% | 29% |

*Avicel is the tradename for Microcrystalline cellulose and sodium carboxymethylcellulose

Note: $\text{Average \% Decrease} = \frac{(\text{Transwell Control} - \text{Formulation})}{\text{Transwell Control}} \times 100$

**EXAMPLE 3: FLUID PROPERTIES CORRELATION TO BARRIER PROPERTIES**

**[0065]** The results show that the barrier properties start forming around 0.4%-0.6% for Avicel RC-591 and for Avicel 611 the barrier properties build from 0.75- 1.75%. The different Avicels have different ratios of the two polymers (Microcrystalline cellulose and sodium carboxymethylcellulose) which would influence the crosslinking density of the hydrogel. This would influence the mesh size of the gel. The change in the mesh size will alter the diffusion of molecules through the gel. It was found that the minimum yield stress has to be above 0.017 Pa-s. The yield stress is the minimal stress that the material needs to have before it flows like a liquid, below that stress it behaves like a solid. Another variable that was found to be an influencer of the barrier properties was Tan(delta). The Tan(delta) is

a measure of the damping ability of a material and is equal to G"/G'. Viscous (loss) modulus, G", is the ability of the material to dissipate energy. Elastic storage modulus, G', is the measure of the elasticity of the material or the ability to store energy. This is evident when looking at the percent blocked versus the fluid properties measured.

**[0066]** From the experiments with Tan(delta) = G"/G', it stands to reason that G' would be a key player, which can be considered as a tortuosity factor. It will be directly related to the crosslink density - either chemical or physical. If there are more crosslinks there will be a higher G' value, which is reflected in the tighter mesh of the matrix giving a smaller Tan(delta), which correlates to better blocking in the model. The matrix becomes a little less flexible as G' increases or Tan(delta) decreases, due to the Tan(delta) having an apparent upper limit. This is thought to be due to the boundaries between truly fluid state and more rigid semi-solid compositions. This is important because the composition is blocking a small molecule such as fluorescein, which acts as a model agent for airborne containments which are larger in size. Due to the increased size of the molecule, diffusion through the gel should be longer in time than fluorescien. The increase time it would take for the larger molecule to transverse the formulation would translate into stopping, dampening, delaying, or impeding the allergic response. This is also important since as the material goes to more of a semisolid, the fluid properties are affected by not being able to spread when dispensed.

**Part 1: Barrier Properties Evaluation of Concentration of Microcrystalline Cellulose and Carboxymethylcellulose**

**[0067]** The pure polymer of microscrystalline cellulose and carboxymethylcellulose was prepared in various concentrations and evaluated using the Transwell flourescent intensity analysis described above with the one exception that the transwell insert was removed at 20 minutes. Two different ratios of microcrystalline cellulose and carboxymethylcellulose was utilized, i.e., the commercial

products Avicel RC-591 and Avicel 611. The data is shown Tables 12, 13, and 14, and displays the effect of the Microcrystalline Cellulose and Carboxymethylcellulose concentration and the ratio's on the barrier properties. The barrier properties of the fluid start to build between 0.4 to 0.6 for Avicel RC-591 and 1.0-1.75 for Avicel 611.

**TABLE 12: Average Fluorescent Intensity (N=3) And Percent Decrease Of Fluorescent Intensity Using Various Concentrations Of Microcrystalline Cellulose And Carboxymethylcellulose (0 – 1.0%)**

| % Concentration* | 0.0 | 0.25 | 0.40 | 0.5 | 0.6 | 0.7 | 0.8 | 0.9 | 1.0 |
|---|---|---|---|---|---|---|---|---|---|
| Intensity (Mean) | 216766 | 212852 | 185110 | 144643 | 50258 | 24219 | 40617 | 15769 | 6736 |
| % Decrease | 0.00 | 1.81 | 14.60 | 33.27 | 76.81 | 88.83 | 81.26 | 92.73 | 96.89 |

*Concentration of Avicel RC-591 (Microcrystalline Cellulose and Carboxymethylcellulose) in formula

**TABLE 13: Average Fluorescent Intensity (N=3) And Percent Decrease Of Fluorescent Intensity Using Various Concentrations Of Microcrystalline Cellulose And Carboxymethylcellulose (1.0 – 5.0%)**

| % Concentration* | 1.0 | 1.25 | 1.5 | 2 | 3 | 4 | 5 |
|---|---|---|---|---|---|---|---|
| Intensity (Mean) | 4530.5 | 944.9 | 85.1 | 62.5 | 503.9 | 1003.2 | 82564.1 |
| % Decrease | 97.91 | 99.56 | 99.96 | 99.97 | 99.77 | 99.54 | 61.91 |

*Concentration of Avicel RC-591 (Microcrystalline Cellulose and Carboxymethylcellulose) in formula

**TABLE 14: Average Fluorescent Intensity (N=2) And Percent Decrease Of Fluorescent Intensity Using Various Concentrations Of Microcrystalline Cellulose And Carboxymethylcellulose (0.25 – 3.0%)**

| % Concentration* | 0 | 0.25 | 0.5 | 0.75 | 1 | 1.25 | 1.75 | 2.25 | 2.5 | 2.75 | 3 |
|---|---|---|---|---|---|---|---|---|---|---|---|

| | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Intensity (Mean) | 198009.1 | 208333.2 | 204114.8 | 202127.5 | 149057.9 | 73064.818 | 4616.052 | 199.72 | 34.741 | 2365.973 | 43.154 |
| % Decrease | 0 | -5.21 | -3.08 | -2.08 | 24.72 | 63.10 | 97.67 | 99.90 | 99.98 | 98.81 | 99.98 |

*Concentration of Avicel 611 (Microcrystalline Cellulose and Carboxymethylcellulose) in formula

**Part 2: Yield Stress, Viscosity and Barrier Properties**

**[0068]** The viscosity of the various concentrations of microcrystalline cellulose and carboxymethylcellulose in the formula was tested. Comparative Formula 7 (containing carageenan) and comparative Formula 6 (containing hypromellose (HPMC)) were also tested for viscosity. The visosity and yield stress data is shown in Table 15. It is found that the minimum yield stress has to be above 0.016 Pa-s for the fluid to have barrier properties with more favorable barrier properties at a yield stress above 0.031 Pa-s. Viscosity was measured at 25°C using a Rheometric Scientific RFSII rheometer with the following parameters (conditions):

Geometry Type = Couette
Cup Diameter = 34.0 [mm]
Bob Diameter = 32.0 [mm]
Bob Length = 33.4 [mm]
Tool Serial Num = 401006
Tool Inertia ..... = 0.0 [g·cm²]
Change Gap to Match Tool Thermal Expansion = Off
Tool Thermal Expansion Coefficient = 0.0 [µm/°C]
Fluid Density..... = 1.0 [g/cm³]

**[0069]** The higher viscosity samples (above 0.8% concentration), the samples were presheared first before the shear rate test. The geometry was also changed to the parallel plate, using the following parameters:

Geometry Type = Parallel Plates (ParaPlate)
Diameter = 25.0 [mm]
Gap = 0.8 [mm]
Read Test Fixture Gap = Off
Tool Serial Num = 0010SS
Tool Inertia ..... = 0.0 [g·cm²]
Change Gap to Match Tool Thermal Expansion = Off
Tool Thermal Expansion Coefficient = 0.0 [µm/°C]
Fluid Density..... = 1.0 [g/cm³]
---
Test Type = Step Rate (Transient) (Step Rate)

Temperature = 25.0 [°C]
Shear Rate = 100.0, 0.0, 0.0, 0.0 [1/s]
Zone Time = 20, 0, 0, 0 [s or h:m:s]
Direction = Counterclockwise
Options = AutoTension
Delay Before Test = Off
Automatically start test when on Temperature = Off
ElectroRheology Mode = Off
Turn OFF Motor = No
Turn Hold ON = No
Turn OFF Temp Controller = No
Set End of Test Temp = No
Analog Data Collection = Off

**TABLE 15: Viscosity Data with Percent Block Fluroescein**

| Sample | Viscosity mean Pa-s | Yield Stress Pa | Percent Blocked Fluorescein |
|---|---|---|---|
| 0.25% Concentration* | 0.004 | 0.003 | 3.3733 |
| 0.40% Concentration* | 0.008 | 0.016 | 14.6033 |
| 0.50% Concentration* | 0.012 | 0.031 | 28.4145 |
| 0.60% Concentration* | 0.017 | 0.053 | 76.8146 |
| 0.70% Concentration* | 0.017 | 0.063 | 88.8271 |
| 0.80% Concentration* | 0.031 | 0.128 | 81.2625 |
| 0.90% Concentration* | 0.045 | 0.382 | 92.7253 |
| 1.00% Concentration* | 0.041 | 0.182 | 97.9100 |
| Formula 2 | 0.045 | 0.275 | 93.0000 |
| Comparative Formula 7 containing Carageenan | 0.022 | 0.023 | 31.5000 |
| Comparative Formula 6 containing Hypromellose | 0.007 | 0 | 0.007 |

*Avicel RC-591 was used for the microcrystalline cellulose and sodium carboxymethylecllulose

**Part 3: Fluid Properties Correlation to Barrier Properties**

**[0070]** The Tan(delta) and complex viscosity of the various concentrations of microcrystalline cellulose and carboxymethylcellulose in the formula was tested. Comparative Formula 7 (containing carageenan) was also tested for viscosity (See FIG. 2). The Tan(delta) and complex viscosity data is shown in Table 15 and graphically shown in FIG. 1. It is found that the maximum Tan(delta) has to be less than 2.5 .1 radians/s with a more favorable barrier properties at a Tan(delta) below1.5 .1 radians/s. Tan(delta) and

complex viscosity was measured at 25°C using a Rheometric Scientific RFSII rheometer with the following parameters (conditions):

Geometry Type = Parallel Plates (ParaPlate)
Diameter = 25.0 [mm]
Gap = 0.8 [mm]
or
Geometry Type = Couette (Couette)
Cup Diameter = 34.0 [mm]
Bob Diameter = 32.0 [mm]
Bob Length = 33.4 [mm]
Tool Serial Num = 401006

Test Type = Dyn Strain Frequency Sweep (DFreqSwp)
*Strain = 0.05 [ ] or lower strain level necessary to be in linear viscoelastic region*
Temperature = 25.0 [°C]
Sweep Mode = Log
Initial Frequency = 0.1 [rad/s]
Final Frequency = 100.0 [rad/s]
Points Per Decade = 3 []
Steady PreShear = Off
PreShear Mode = Preshear Off
Delay Before Test = On
Delay Before Test = 60 [s or h:m:s]

Automatically start test when on Temperature = Off
AutoTension Adjustment = Off
Mode = Apply Constant Static Force
AutoStrain = Off

Strain Amplitude Control = Default Behavior
Limit Minimum Dynamic Force Used = No

Measurement Options = Default Delay Settings
Cycles = 0.5 []
Correlation: One Cycle Correlate = Off

Turn OFF Motor = No
Turn Hold ON = No
Turn OFF Temp Controller = No
Set End of Test Temp = No
Steady Stress on Dynamic = 0.0 [Pa]
Analog Data Collection = Off

**TABLE 16: Barrier Properties, Tan(Delta), And Complex Viscosity (N*)**

| Sample | Percent Blocked Fluorescein | Tan(delta) | n* |
|---|---|---|---|
| | | .1 radians/s | Pa-s |
| A591 0.5% | 28.4145 | 2.5 | 0.04 |
| A591 0.6% | 76.8146 | 1.1 | 0.163 |
| A591 0.9% | 92.7253 | 0.41 | 1.7 |
| A591 1% | 97.9100 | 0.37 | 2.7 |
| A611 1.25% | 24.7217 | 4.3 | 0.143 |
| A611 1.75% | 63.1003 | 1.2 | 0.642 |
| Formula 2 | 99.2018 | 0.45 | 7.8 |
| Formula 7 containing Carageenan (Comparative) | 31.5000 | 4.3 | 0.039 |

*A591= Avicel RC-591 and A611=Avicel CL611 was used for the microcrystalline cellulose and sodium carboxymethylecllulose

## EXAMPLE 4: IN-VITRO NOSE MODEL

**[0071]** The silicon model shown in FIG. 3 was coated with 1% PolyOx to simulated mucin in the nasal cavity. The test article was prepared with the inclusion of a dye in the formulation to create contrast for where the formulation was deposited. The test article was then inserted into Area 1 at an angle of 45 degrees. The test article is depressed the appropriate number of times to simulate usage, at this time the product is sprayed out and deposited on the walls of the in vitro nose model. The model is taken apart and analysis of where the deposition is conducted.

**[0072]** Using this test method, the initial deposition pattern was determined. This was done looking at uniformity of coverage inside the nasal cavity and how the angle of the nasal spray affects deposition. Various pump configurations with different formulations were investigated. The data is shown in Table 17.

**TABLE 17: In Vitro Nose Model Deposition Data**

| Formula | Polymers | Pump Selection (Manufacturer,Type) | Front (%) | Main Area (%) | Olfactory (%) | Post (%) |
|---|---|---|---|---|---|---|
| 1 | Avicel and PVP | Pfeiffer, High Viscosity Pump | 62.54 | 31.33 | 5.08 | 1.05 |
| 1 | Avicel and PVP | Calmar, High Viscosity 60 Pump | 34.44 | 47.49 | 17.01 | 1.07 |
| 1 | Avicel and PVP | Calmar, High Viscosity 90 Pump | 18.73 | 69.4 | 6.82 | 5.04 |
| 1 | Avicel and PVP | Calmar, WIDE pump | 16.03 | 72.96 | 9.24 | 1.78 |

**[0073]** While the invention has been described above with reference to specific embodiments thereof, it is apparent that many changes, modifications, and variations can be made without departing from the inventive concept disclosed herein. Accordingly, it is intended to embrace all such changes, modifications, and variations that fall within the spirit and broad scope of the appended claims. All patent applications, patents, and other publications cited herein are incorporated by reference in their entirety.

WHAT IS CLAIMED IS:

1. A method of blocking or trapping allergens or allergen particles in the nasal cavity of a subject, comprising the steps of:

applying to the nasal cavity of the subject a nasal composition comprising microcrystalline cellulose; and

sodium carboxymethylcellulose and its salt derivatives thereof,

wherein the microcrystalline cellulose to sodium carboxymethylcellulose are present in a ratio of about 50:50 to about 99:1, respectively, and

wherein the nasal composition is substantially free of active pharmaceutical ingredients.

2. The method of claim 1, wherein the ratio of microcrystalline cellulose to sodium carboxymethylcellulose is about 70:30 to about 99:1.

3. The method of claim 1, wherein the ratio of microcrystalline cellulose to sodium carboxymethylcellulose is about 85:15 to about 90:10.

4. The method of claim 1, wherein the microcrystalline cellulose and sodium carboxymethylcellulose are included in the composition in a combined amount of at least about 0.5 wt.% based on the total weight of the composition.

5. The method of claim 1, wherein the microcrystalline cellulose and sodium carboxymethylcellulose are included in the composition in a combined amount from about 0.5 wt.% to about 10 wt.% based on the total weight of the composition.

6. The method of claim 1, wherein the nasal gel composition further comprises a compound selected from the group consisting of polyvinylpyrrolidone and/or derivatives thereof, carageenan, hypromellose, hydroxypropylcellulose, polyvinyl alcohol, methacrylates, polyethylene oxide, gellan gum, acacia, alginic acid, bentonite, carbomers, carboxymethylcellulose. ethylcellulose, gelatin, hydroxyethylcellulose, magnesium aluminum silicate, methylcellulose, poloxamers, sodium alginate, tragacanth, xanthan gum,

guar gum, clays, Sodium acrylate/acryloyldimethyl taurate copolymer & Isohexadecane & Polysorbate 80, poly(ethylene oxide) polymers, cross-linked copolymer of Vinyl Pyrrolidone and Acrylic Acid, synthetic high molecular weight polymers of acrylic acid, fucoidan, locust bean gum, and mixtures thereof.

7. The method of claim 1, wherein the nasal gel composition further comprises polyvinylpyrrolidone and/or derivatives thereof having an average molecular weight in the range of about 1,500 to about 3,000,000 g/mol.

8. The method of claim 7, wherein the polyvinylpyrrolidone and/or derivatives thereof has an average molecular weight in the range of about 2,500 to about 500,000 g/mol.

9. The method of claim 7, wherein the polyvinylpyrrolidone and/or derivatives thereof is present in at least about 0.5% by weight of the composition.

10. The method of claim 7, wherein the polyvinylpyrrolidone and/or derivatives thereof in an amount from about 0.5 wt.% to about 30 wt.%.

11. The method of claim 7, wherein the polyvinylpyrrolidone and/or derivatives thereof is present in between about 2% and about 30% by weight of the composition.

12. The method of claim 7, wherein the polyvinylpyrrolidone and/or derivatives thereof is present in between about 5% and about 25% by weight of the composition.

13. The method of claim 1, wherein the composition has a yield stress of at least about 0.016 Pa at 25 °C using a Rheometric Scientific RFSII rheometer.

14. The method of claim 1, wherein the composition has a yield stress of at least about 0.031 Pa at 25 °C using a Rheometric Scientific RFSII rheometer.

15. The method of claim 1, wherein the composition has a yield stress of at least about 0.053 Pa at 25 °C using a Rheometric Scientific RFSII rheometer.

16. The method of claim 1, wherein the composition further comprises at least one optional component selected from the group consisting of a sensate, buffering agent, surfactant, polyethylene glycol, glycerin, preservative, color, flavor and mixtures thereof.

17. The method of claim 16, wherein the sensate agent is a cooling flavor.

18. The method of claim 1, wherein the composition is a liquid prior to dispensing.

19. The method of claim 1, wherein the composition is a gel after dispensing.

20. The method of claim 1, wherein the composition exhibits a decrease in fluorescent intensity from a standard of at least about 15% as compared to a fluorescein sodium salt dye standard, as measured by transwell plate diffusion.

21. The method of claim 1, wherein the composition exhibits a decrease in fluorescent intensity from a standard of at least about 33% as compared to a fluorescein sodium salt dye standard, as measured by transwell plate diffusion.

22. The method of claim 1, wherein the composition exhibits a decrease in fluorescent intensity from a standard of at least about 76% as compared to a fluorescein sodium salt dye standard, as measured by transwell plate diffusion.

23. The method of claim 1, wherein the composition is applied via a pump, finger, swab or tube.

24. The method of claim 1, wherein the composition is applied to the inferior meatus and middle meatus of the nasal cavity.

25. The method of claim 1, wherein at least about 30% by weight of the composition is applied to the inferior meatus and middle meatus of the nasal cavity.

26. The method of claim 1, wherein at least about 50% by weight of the composition is applied to the inferior meatus and middle meatus of the nasal.

27. The method of claim 1, wherein the composition is applied as often as needed.

28. The method of claim 1, wherein the composition is capable of blocking allergens for at least about one hour.

29. The method of claim 1, wherein about 60% of users perceive a reduction in allergy symptoms.

30. The method of claim 1, wherein about 70% of users perceive a reduction in allergy symptoms.

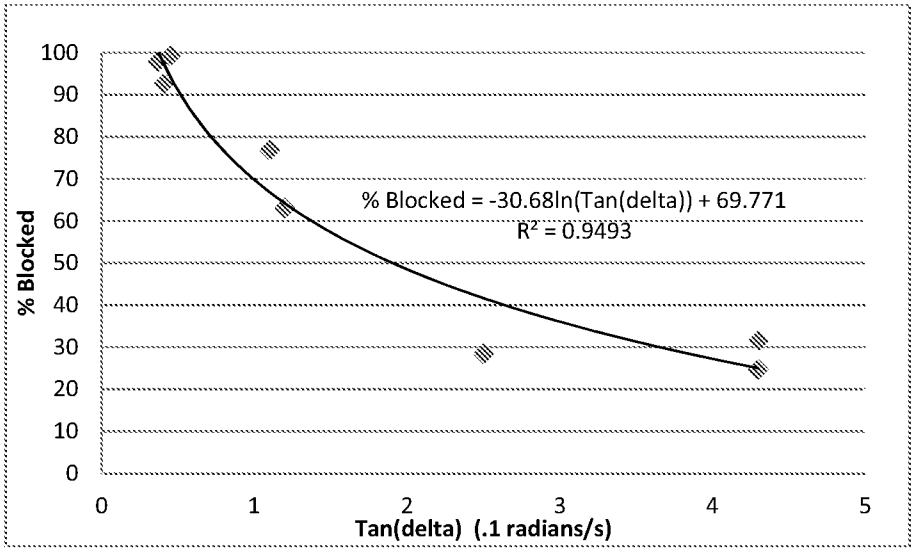

100
90
80
70
60
50
40
30
20
10
0
% Blocked
% Blocked = -30.68ln(Tan(delta)) + 69.771
R² = 0.9493
0
1
2
3
4
5
Tan(delta) (.1 radians/s)

FIG. 1

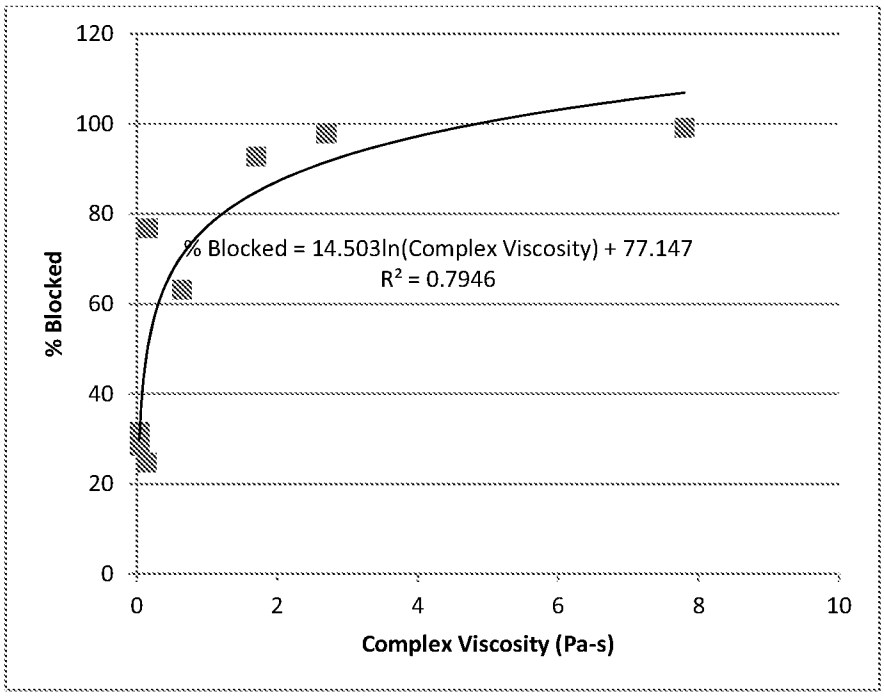
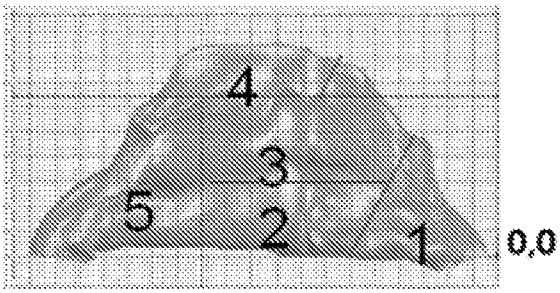

120
100
80
60
40
20
0
% Blocked
% Blocked = 14.503ln(Complex Viscosity) + 77.147
R² = 0.7946
0
2
4
6
8
10
Complex Viscosity (Pa-s)

FIG. 2




**Area 1: Front of the nose. Prior to nasal valve**
**Area 2: inferior of nasal cavity (inferior meatus)**
**Area 3: middle part of nasal cavity (middle meatus)** } **Targeted areas for coverage**
Area 4: olfactory region (superior meatus)
Area 5: posterior of nasal cavity, toward nasopharyngeal } areas to avoid

FIG. 3

# INTERNATIONAL SEARCH REPORT

International application No
PCT/US2012/057870

A. CLASSIFICATION OF SUBJECT MATTER
INV. A61P37/08 A61K9/00 A61K47/38
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, WPI Data, BIOSIS, CHEM ABS Data, EMBASE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

| Category* | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|---|---|---|
| X | WO 02/051379 A2 (IMPETUS AG [CH]; JAENICKE CHRISTOF [DE]) 4 July 2002 (2002-07-04) Paragraph linking pages 4-5 page 8, paragraph 2-3 | 1-30 |
| A | US 6 565 832 B1 (HASLWANTER JOSEPH A [US] ET AL) 20 May 2003 (2003-05-20) column 1, line 6 - column 2, line 37 column 3, line 45 - column 4, line 32; claims; examples 1-2 page 10, line 3 - page 11, line 27; claim 2 | 1-30 |
| A | US 6 780 398 B1 (AKUTSU RIKA [JP] ET AL) 24 August 2004 (2004-08-24) column 1, line 8 - column 2, line 51 column 3, lines 49-59; claims 4-8; example 1 | 1-30 |

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

[X] See patent family annex.

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"&" document member of the same patent family

| Date of the actual completion of the international search | Date of mailing of the international search report |
|---|---|
| 14 December 2012 | 22/01/2013 |

| Name and mailing address of the ISA/ | Authorized officer |
|---|---|
| European Patent Office, P.B. 5818 Patentlaan 2<br>NL - 2280 HV Rijswijk<br>Tel. (+31-70) 340-2040,<br>Fax: (+31-70) 340-3016 | Paul Soto, Raquel |

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# INTERNATIONAL SEARCH REPORT

International application No
PCT/US2012/057870

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

| Category* | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|---|---|---|
| A | WO 92/14473 A1 (FISONS AG [CH])<br>3 September 1992 (1992-09-03)<br>page 3, line 23 - page 5, line 29; claims 6-9 | 1-30 |
| A | DE 41 17 887 A1 (ROCHLER SIEGFRIED [DE])<br>12 December 1991 (1991-12-12)<br>the whole document | 1-30 |
| A | US 2003/161899 A1 (THEISS PETER [DE])<br>28 August 2003 (2003-08-28)<br>the whole document | 1-30 |

2

# INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/US2012/057870

| Patent document cited in search report | Publication date | Patent family member(s) | Publication date |
|---|---|---|---|
| WO 02051379 A2 | 04-07-2002 | AT 326947 T | 15-06-2006 |
| | | DE 10064950 A1 | 11-07-2002 |
| | | DK 1343472 T3 | 25-09-2006 |
| | | EP 1343472 A2 | 17-09-2003 |
| | | ES 2266288 T3 | 01-03-2007 |
| | | PT 1343472 E | 31-10-2006 |
| | | WO 02051379 A2 | 04-07-2002 |
| US 6565832 B1 | 20-05-2003 | CA 2333442 A1 | 31-07-2001 |
| | | US 6565832 B1 | 20-05-2003 |
| | | US 2003185763 A1 | 02-10-2003 |
| US 6780398 B1 | 24-08-2004 | AT 240717 T | 15-06-2003 |
| | | AU 6471500 A | 05-03-2001 |
| | | DE 60002885 D1 | 26-06-2003 |
| | | DE 60002885 T2 | 11-03-2004 |
| | | EP 1200066 A1 | 02-05-2002 |
| | | ES 2199845 T3 | 01-03-2004 |
| | | JP 2003506396 A | 18-02-2003 |
| | | US 6780398 B1 | 24-08-2004 |
| | | WO 0110409 A1 | 15-02-2001 |
| WO 9214473 A1 | 03-09-1992 | AU 1247192 A | 15-09-1992 |
| | | BE 1004177 A4 | 06-10-1992 |
| | | CN 1065010 A | 07-10-1992 |
| | | FR 2673104 A1 | 28-08-1992 |
| | | GR 1001511 B | 28-02-1994 |
| | | IE 920516 A1 | 26-08-1992 |
| | | IT 1254627 B | 28-09-1995 |
| | | PT 100150 A | 31-05-1993 |
| | | WO 9214473 A1 | 03-09-1992 |
| | | ZA 9201247 A | 28-10-1992 |
| DE 4117887 A1 | 12-12-1991 | NONE | |
| US 2003161899 A1 | 28-08-2003 | AT 493112 T | 15-01-2011 |
| | | AU 6750401 A | 11-12-2001 |
| | | BG 64887 B1 | 31-08-2006 |
| | | BG 104714 A | 31-05-2002 |
| | | BR 0003852 A | 23-07-2002 |
| | | CA 2413188 A1 | 06-12-2001 |
| | | CZ 20003062 A3 | 16-01-2002 |
| | | DE 20009841 U1 | 25-10-2001 |
| | | EE 200000375 A | 15-02-2002 |
| | | EP 1159958 A1 | 05-12-2001 |
| | | EP 1286657 A1 | 05-03-2003 |
| | | HR P20000559 A2 | 31-12-2001 |
| | | HU 0003408 A2 | 28-09-2002 |
| | | JP 2001342131 A | 11-12-2001 |
| | | JP 2006316063 A | 24-11-2006 |
| | | PL 342179 A1 | 03-12-2001 |
| | | RU 2237468 C2 | 10-10-2004 |
| | | SK 12812000 A3 | 03-12-2001 |
| | | UA 72734 C2 | 17-12-2001 |
| | | US 2002082305 A1 | 27-06-2002 |
| | | US 2003161899 A1 | 28-08-2003 |
| | | US 2012308671 A1 | 06-12-2012 |
| | | WO 0191719 A1 | 06-12-2001 |

# INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/US2012/057870

| Patent document cited in search report | Publication date | Patent family member(s) | Publication date |
|---|---|---|---|
| ---------- | | | |