US006565832B1

(12) **United States Patent**
Haslwanter et al.

(10) **Patent No.: US 6,565,832 B1**
(45) **Date of Patent: May 20, 2003**

(54) **SPRAY COMPOSITION WITH REDUCED DRIPPING**

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(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.

(21) Appl. No.: **09/494,574**

(22) Filed: **Jan. 31, 2000**

(51) **Int. Cl.**[7] **A61K 9/12**; A61K 9/08

(52) **U.S. Cl.** **424/45**; 424/78.04; 424/434; 514/853

(58) **Field of Search** 424/45, 78.04, 424/78.08, 601, 434; 514/912, 853, 937

(56) **References Cited**

U.S. PATENT DOCUMENTS

5,854,269	A	*	12/1998	Haslwanter et al.
5,897,858	A	*	4/1999	Haslwanter et al.
5,976,573	A	*	11/1999	Kim
6,368,616	B1	*	4/2002	Doi 424/434

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(57) **ABSTRACT**

An aqueous-based sprayable composition comprises a therapeutic or palliative agent, water and a mixture of microcrystalline cellulose and alkali metal carboxyalkylcellulose. In one embodiment, the composition is a non-Newtonian nasal spray exhibiting a very rapid viscosity recovery upon removal of shear forces.

5 Claims, 2 Drawing Sheets

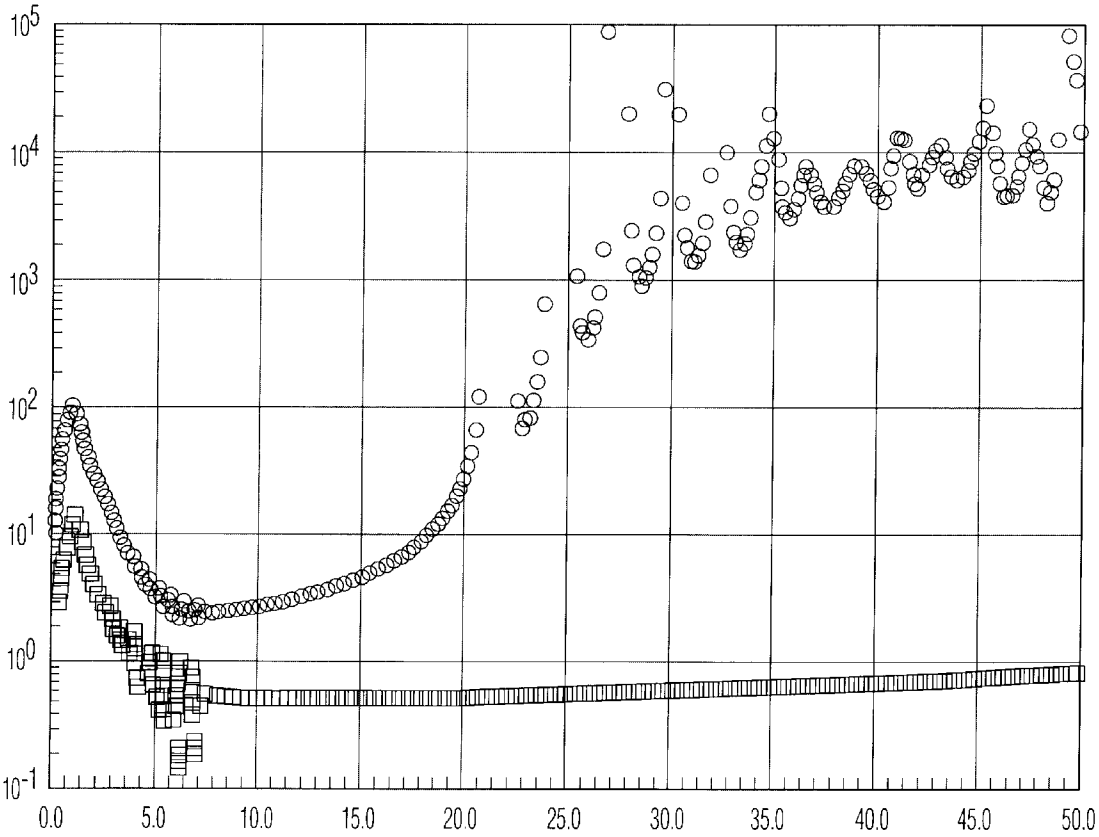


Exhibit 1155

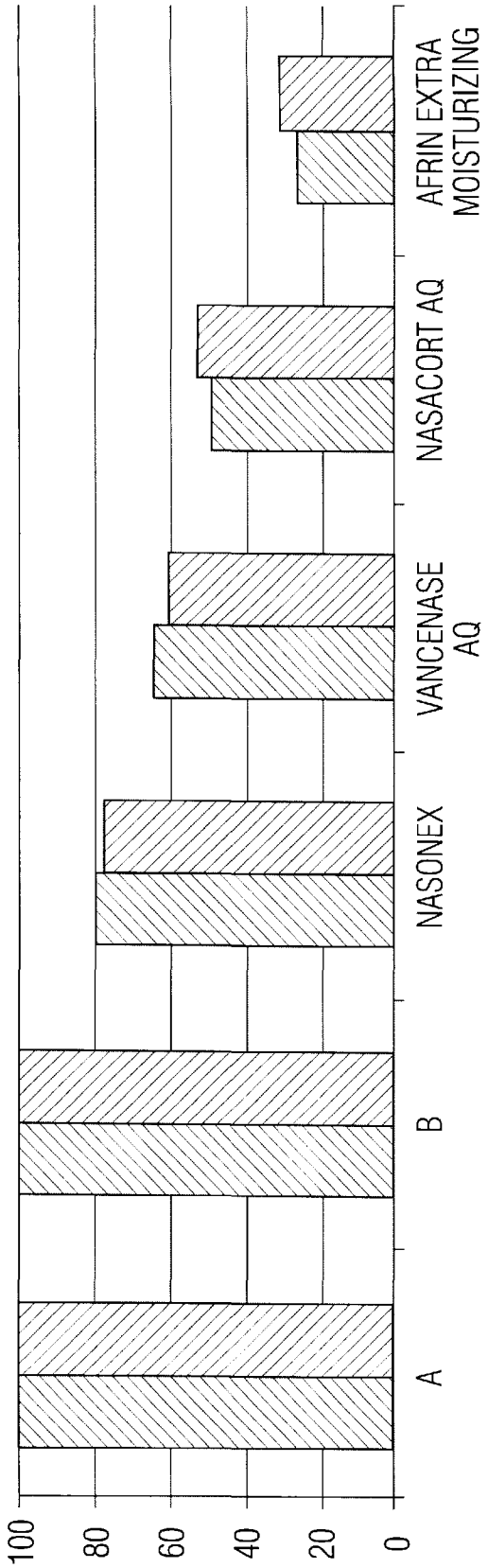
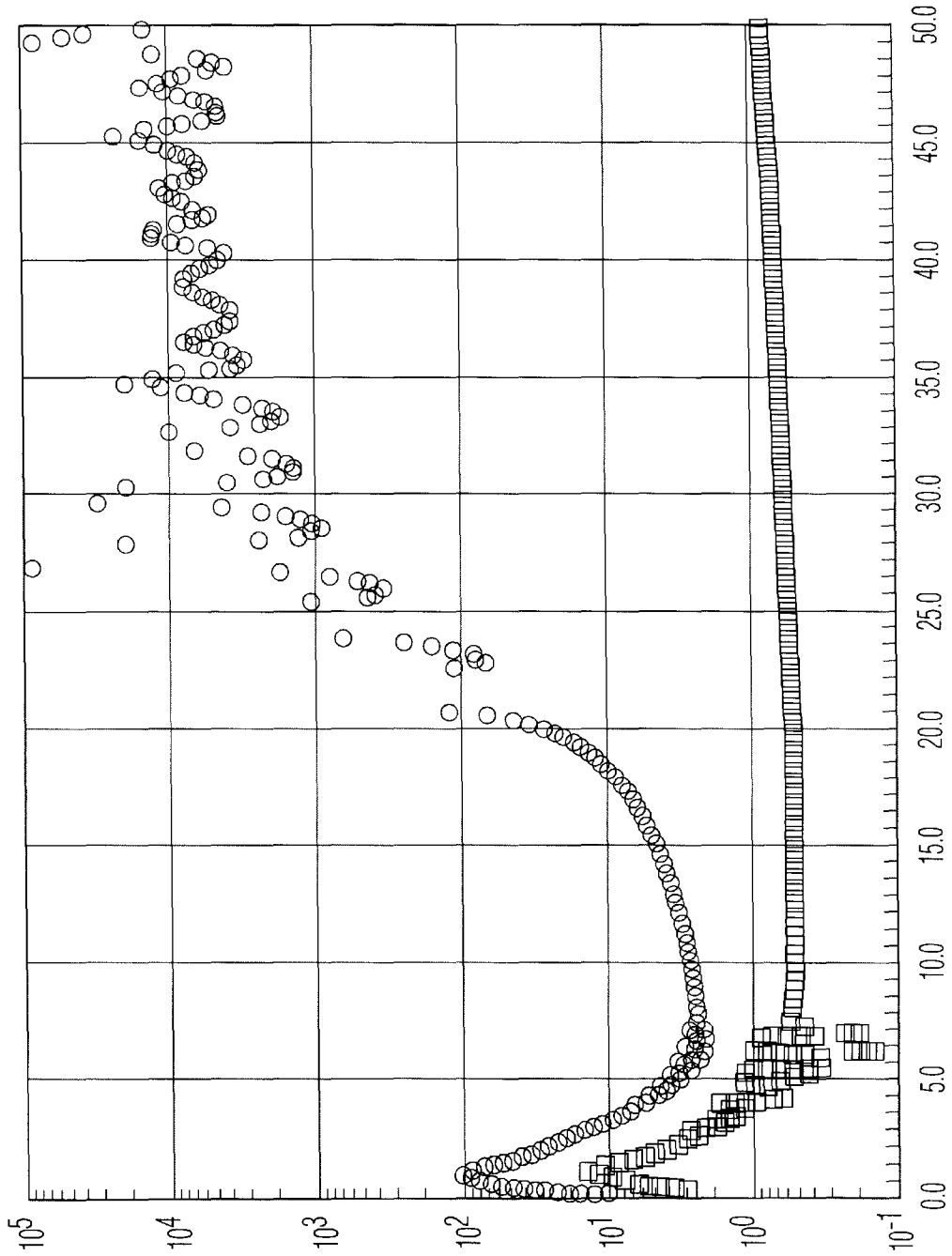


FIG. 1

FIG. 2



SPRAY COMPOSITION WITH REDUCED DRIPPING

INTRODUCTION TO THE INVENTION

The present invention relates to the field of fluid compositions for application to the body, and more particularly to spray compositions which have a reduced tendency to run or drip.

Nasal sprays have been used for many years by persons suffering from nasal disorders, such as infections or allergic manifestations. Among the pharmaceutical agents commonly delivered intranasally are antihistamines, antiinflammatory drugs, decongestants, antimuscarinics, antibiotics, anesthetics and moisturizers. In addition, it is possible to deliver agents intranasally to achieve systemic effects through absorption across the well-vascularized mucosal membranes; certain vaccines, analgesics and other prophylactic or therapeutic substances can be efficiently administered in this manner.

Various spray compositions are also known for application other than intranasally, such as breath freshener and analgesic sprays for the mouth and pharynx and antiseptic sprays for skin application of medicinal or cosmetic compositions.

A common problem with spray administration is a low efficiency of the active agent, since the structure of body cavities and parts does not typically facilitate retention of the applied formulation. This is particularly the case for aqueous-base nasal spray formulations, which must have sufficient fluidity to be dispensed by a pump device or a squeeze-type spray bottle, but which can simply drain from the nose or pass through the nose and into the pharynx while, or immediately after, being sprayed. Moreover, due to ciliation of the nasal passages and movement of air through the nose, even materials applied in particulate form, such as by a pressurized metered dose inhaler or a powdered drug inhaler, are rapidly cleared from the nose. Several of the possible active agents or other formulation components have a quite unpleasant taste, so it is desirable to minimize the amount of the formulation which is not retained within the nose for at least the minimum time required to obtain the desired effect. Due to swallowing of much of the formulation which enters the oropharyngeal area, a large portion of the active agent introduced into the nose is generally rendered unavailable for its intended use.

Aqueous materials sprayed onto the oral, rectal or vaginal mucosa, or onto the skin, similarly have a tendency to run or drip, and therefore frequently are not retained in a desired location for sufficient time to accomplish the desired function, which may involve absorption of an active agent by the underlying tissues for a local or systemic effect.

International Patent Application WO 94/05330 describes a nasal spray product that forms a gel upon contact with mucous membranes, which product contains a crosslinked acrylic acid-based polymer. The product is alleged to exhibit a reduced tendency for "roll-back," where liquid exits the nose after spray application.

The product Nasacor™ AQ nasal spray is an aqueous suspension of particles of the corticosteroid drug triamcinolone acetonide, and contains about 2 percent by weight of a mixture of microcrystalline cellulose and carboxymethylcellulose sodium, as a suspending agent. Such suspensions are described in U.S. Pat. No. 5,976,573.

The product Vancenase™ AQ nasal spray is an aqueous suspension of the corticosteroid drug beclomethasone dipropionate monohydrate, containing about 1.5 percent by weight of a mixture of microcrystalline cellulose and carboxymethylcellulose sodium, as a suspending agent.

The product Nasonex™ nasal spray is an aqueous suspension of the corticosteroid drug mometasone furoate monohydrate, containing about 2 percent by weight of a mixture of microcrystalline cellulose and carboxymethylcellulose sodium, as a suspending agent.

It would be desirable to provide an aqueous composition that can be made to have a viscosity sufficiently low to permit spraying with a standard pump mechanism or squeeze-type spray bottle, but which then rapidly exhibits a significant viscosity increase to retain the composition at the application site.

SUMMARY OF THE INVENTION

The present invention provides an aqueous-based sprayable composition containing a therapeutic or palliative agent, water and a mixture of microcrystalline cellulose and alkali metal carboxyalkylcellulose. The composition is a non-Newtonian, or thixotropic, fluid, exhibiting a reduced apparent viscosity while being subjected to shear forces, but a high apparent viscosity while at rest; this property permits application by spraying with readily available pump spray devices or squeeze-type spray bottles immediately following the application of a shearing force (such as those created by vigorously shaking the product container), but causes the sprayed material to remain at least temporarily relatively immobile on mucosal membranes or the skin. The preferred embodiments have a very rapid rate of viscosity recovery, following withdrawal of the shearing force.

The invention can be used to prepare many types of spray compositions, such as those for application to mucous membranes or the skin. In a particularly preferred form, the invention is an aqueous nasal spray containing a topically active decongestant.

BRIEF DESCRIPTION OF THE DRAWINGS

FIG. **1** is a graphical representation of the results of the experiment described in Example 4.

FIG. **2** is a graphical representation of the results of the experiment described in Example 5.

DETAILED DESCRIPTION OF THE INVENTION

The essential components of the composition of the present invention are water, a therapeutic or palliative agent and a mixture of microcrystalline cellulose and an alkali metal carboxyalkylcellulose. It is contemplated that the composition will be useful for delivering agents by spraying; it is an advantage of the invention that the composition, after spraying, has a minimal tendency to drip or run from the surface to which it is applied.

Typically, purified water, such as that treated by distillation, deionization or reverse osmosis techniques will be used, it generally being desired to minimize formulation characteristic variations which may occur when the water supply is not very consistent in its chemical makeup. Preferred waters include those having the specifications of the official monograph for "Purified Water" in the current *United States Pharmacopeia*, published by United States Pharmacopeial Convention, Inc., Rockville, Md. U.S.A. In those instances where microbial contamination must be prevented, such as for antiseptic skin sprays, sterile water will be used and any of the customary preservatives will be added.

Numerous classes of pharmaceutical active agents are suitable for inclusion in the thixotropic formulation of the invention. Agents for delivery intranasally include antihistamines, antiinflammatory drugs, decongestants, antimuscarinics, antibiotics, anesthetics and moisturizers. Orally delivered agents include antibiotics, analgesics, anesthetics and moisturizers. Agents which are delivered vaginally or rectally include antiemetics, antibiotics (including antimycotic agents), analgesics and anesthetics. For topical application to the skin, useful active agents include sunscreening agents, local anesthetics and antimicrobials. These lists are not intended to be exhaustive, as many other types of active agents can beneficially be incorporated into the inventive formulations. Frequently, it will be desired to incorporate a mixture of two or more active agents, sometimes including more than one class of such agents, in a composition.

Particularly efficacious in the nasal spray compositions of the present invention are the sympathomimetic amine nasal decongestants. Those currently approved for topical use in the United States include, without limitation, levmetamfetamine (also known as 1-desoxyephedrine), ephedrine, ephedrine hydrochloride, ephedrine sulfate, naphazoline hydrochloride, oxymetazoline hydrochloride, phenylephrine hydrochloride, propylhexedrine and xylometazoline hydrochloride. Levmetamfetamine and propylhexidrine are typically administered by inhalation, being dispersed in air, so are candidates for pressurized aerosol formulation, while the other compounds are usually administered topically in aqueous solutions or jellies, in concentrations differing for the individual drugs, but typically not exceeding about 1 percent by weight.

Specific drugs that may be incorporated when the composition is intended to relieve oropharyngeal discomfort, such as sore throat, cold or canker sores, painful gums and other conditions are topical anesthetics such as phenol, hexylresorcinol, salicyl alcohol, benzyl alcohol, dyclonine, dibucaine, benzocaine, buticaine, cetylpyridinium chloride, diperidon, clove oil, menthol, camphor, eugenol and others. Similarly, drugs that may be incorporated for application to the skin for relieving discomfort include lidocaine, benzocaine, tetracaine, dibucaine, pramoxine, diphenhydramine, benzyl alcohol, hydrocortisone, betamethasone, mometasone and others.

Mixtures of microcrystalline cellulose and an alkali metal carboxyalkylcellulose are commercially available, the mixture presently preferred for use in this invention being sold by FMC Corporation, Philadelphia, Pa. U.S.A. as Avicel™ RC-591. This material contains approximately 89 weight percent microcrystalline cellulose and approximately 11 weight percent sodium carboxymethylcellulose, and is known for use as a suspending agent in preparing various pharmaceutical suspensions and emulsions. However, there previously has been no reported application for this material in compositions which otherwise have no suspended particulates, i.e., which compositions are solutions. The compositions of the present invention contain at least about 2.5 weight percent of the cellulose/carboxyalkylcellulose compound mixture, generally not exceeding about 10 weight percent to avoid producing high viscosities which impede spraying with the usual devices. Preferably, about 2.5 to about 5 percent of the mixture will be included. More preferably, the amount will be about 2.5 to about 3.5 weight percent.

A closely related mixture is available from the same source as Avicel™ RC-581, having the same bulk chemical composition as the RC-591, and this material is also useful in the invention. Microcrystalline cellulose and alkali metal carboxyalkylcellulose are commercially available separately, and can be mixed in desired proportions for use in the invention, with the amount of microcrystalline cellulose preferably being between about 85 and about 95 weight percent of the mixture for both separately mixed and co-processed mixtures. However, performance of the inventive composition appears to generally be better when the co-processed mixtures are used.

When the compositions of the invention are intended for application to sensitive mucosal membranes, it will usually be desirable to adjust the pH to a relatively neutral value, using an acid or base, unless the natural pH already is suitable. In general, pH values about 4 to about 8 are preferred for tissue compatibility; the exact values chosen should also promote chemical and physical stability of the composition. In some instances, buffering agents will be included to assist with maintenance of selected pH values; typical buffers are well known in the art and include, without limitation thereto, phosphate, citrate and borate salt systems.

Depending on the intended application, it may be desirable to incorporate up to about 10 percent by weight, more typically about 0.5 to about 5 weight percent, of an additional rheology-modifying agent, such as a polymer or other material. Useful materials include, without limitation thereto, sodium carboxymethyl cellulose, algin, carageenans, carbomers, galactomannans, hydroxypropyl methylcellulose, hydroxypropyl cellulose, polyethylene glycols, polyvinyl alcohol, polyvinylpyrrolidone, sodium carboxymethyl chitin, sodium carboxymethyl dextran, sodium carboxymethyl starch and xanthan gum. Combinations of any two or more of the foregoing are also useful.

The compositions may further contain any of a number of optional components, such as humectants, preservatives and aromatic substances. Humectants, which are hygroscopic materials such as glycerin, a polyethylene or other glycol, a polysaccharide and the like act to inhibit water loss from the composition and may add moisturizing qualities. Useful aromatic substances include camphor, menthol, eucalyptol and the like, and fragrances. Preservatives are typically incorporated to establish and maintain a freedom from pathogenic organisms; representative components include benzyl alcohol, methylparaben, propylparaben, butylparaben, chlorobutanol, phenethyl alcohol (which also is a fragrance additive), phenyl mercuric acetate and benzalkonium chloride.

The more simple techniques commonly used to determine rheological properties of fluid compositions, including the Brookfield rotating kinematic viscometer which measures torque transmitted through a sample using a rotating spindle, do not yield the most meaningful information for non-Newtonian fluids such as those of this invention. Since the viscosity of the thixotropic composition varies inversely according to the magnitude of shear force being applied, and the viscosity increases over time following withdrawal of the shear force, it is more useful to measure and compare complex viscosity. A mathematical derivation of complex viscosity can be found in H. A. Barnes et al., *An Introduction to Rheology*, Elsevier, N.Y. 1989, particularly at pages 46–48. Complex viscosity from a oscillatory applied shear is defined by these authors at page 48 as being: "the ratio of the shear stress . . . to the rate of shear. . . . " Units for expressing complex viscosity (typically represented by the symbol η^*) are in Pascal seconds (Pa.s.), equivalent to newton seconds/meter^2 in the International System of Units.

The composition of the invention has a shear viscosity sufficiently low to permit spraying with the customary

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