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TITLE

ALBUTEROL SULFATE SUSPENSION AEROSOL FORMULATIONS

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ALBUTEROL SULFATE SUSPENSION AEROSOL FORMULATIONS

BACKGROUND OF THE INVENTION

FIELD OF THE INVENTION

This invention relates to suspension aerosol formulations suitable for the administration of medicaments. In another aspect, it relates to pharmaceutical suspension aerosol formulations containing albuterol sulfate and in yet another aspect to aerosol formulations using 1,1,1,2,3,3,3-heptafluoropropane as the propellant.

DESCRIPTION OF THE RELATED ART

Albuterol sulfate is a relatively selective beta-2 adrenergic bronchodilator. It is available in a variety of dosage forms including tablets, syrups and formulations suitable for inhalation. For example, VENTOLIN™ Inhalation Aerosol (commercially available from Allen & Hansburys, Division of Glaxo Inc.; Research Triangle Park, NC) is a metered-dose aerosol unit containing a microcrystalline suspension of albuterol (free base) in propellant (a mixture of trichloromonofluoromethane and dichlorodifluoromethane) with oleic acid. VENTOLIN ROTOCAPS™ for Inhalation (commercially available from Allen & Hansburys) contain a mixture of microfine albuterol sulfate with lactose and are intended for use with a specially designed device for inhaling powder. VENTOLIN™ Solution for Inhalation (commercially available from Allen & Hansburys) is an aqueous solution of albuterol sulfate intended for use with a nebulizer.

Chlorofluorocarbons, including trichloromonofluoromethane and dichlorodifluoromethane, have been implicated in the destruction of the ozone layer and their production is being phased out. Hydrofluorocarbon 227 (1,1,1,2,3,3,3-heptafluoropropane) is viewed as being less destructive to ozone than many

chlorofluorocarbon propellants; furthermore, it has a low toxicity and a vapor pressure suitable for use in aerosols.

Patent Applications WO 91/11495 and WO 91/11496 (both to Weir) describe pharmaceutical suspension aerosol formulations comprising a medicinal agent, optionally a surfactant, and a propellant mixture containing a partially fluorinated lower alkane. The patent application specifically discloses an aerosol formulation containing (indicated in percentage by weight) 0.3% salbutamol, 0.2% Span 85, 20.0% pentane, 30.0% 1,1,1,2,3,3,3-heptafluoropropane and 49.5% 1,1,1,2-tetrafluoroethane. The patent application does not, however, disclose or suggest the use of ethanol as a component in combination with 1,1,1,2,3,3,3-heptafluoropropane.

European Patent Office Publication 0 384 371 (Heiskel) discloses solution aerosols in which 1,1,1,2,3,3,3-heptafluoropropane in combination with at least one of propane, butane, isobutane, dimethylether, and 1,1-difluoroethane serves as the propellant. The application does not, however, disclose suspension aerosols or pharmaceutical aerosol formulations.

Patent Application WO 91/02056 (Schultz et al.) describes suspension aerosol formulations comprising a medicinal agent, a member of a particular class of perfluorinated surface-active dispersing agent, and 1,1,1,2,3,3,3-heptafluoropropane. Albuterol sulfate is recited as a suitable medicinal agent. The patent application does not, however, teach or suggest the use of ethanol in combination with 1,1,1,2,3,3,3-heptafluoropropane.

SUMMARY OF THE INVENTION

This invention provides suspension aerosol formulations comprising a therapeutically effective amount of micronized albuterol sulfate and 1,1,1,2,3,3,3-heptafluoropropane as substantially the only propellant. This invention also provides suspension aerosol formulations comprising a therapeutically effective amount of micronized albuterol sulfate, from about 0.1 to about 15

percent by weight of ethanol, and 1,1,1,2,3,3,3-heptafluoropropane as substantially the only propellant. This invention also provides suspension aerosol formulations comprising a therapeutically effective amount of micronized albuterol sulfate, from about 5 to 15 percent by weight of ethanol, from about 0.05 to about 0.5 percent by weight of a surfactant selected from the group consisting of oleic acid and sorbitan trioleate, and 1,1,1,2,3,3,3-heptafluoropropane as substantially the only propellant. This invention also provides a method for inducing bronchodilation in a mammal, comprising the step of administering to the mammal a formulation as described above by inhalation.

DETAILED DESCRIPTION OF THE INVENTION

All weight percentages recited herein are based on the total weight of the formulation unless otherwise indicated.

The term "suspension aerosol" means that the albuterol sulfate is in particulate form and the formulation is substantially free of dissolved albuterol sulfate.

The term "micronized" means that the albuterol sulfate is in the form of a fine powder, that is, over 90 percent of the particles will have a diameter of less than about 10 microns.

The formulations of the invention contain a therapeutically effective amount of micronized albuterol sulfate. Preferably micronized albuterol sulfate constitutes about 0.2 to about 0.5 percent by weight, more preferably from about 0.35 to about 0.42 percent by weight of the aerosol formulation.

Ethanol can optionally be included in a formulation of the invention. When ethanol is present it constitutes from about 0.1 to about 20 percent by weight, preferably from about 5 to about 15 percent by weight of the formulation. A surfactant selected from the group consisting of oleic acid and sorbitan trioleate can also optionally be included in the formulation when the

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