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Ingebrethsen

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[54] **AEROSOL DELIVERY ARTICLE**

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[52] **U.S. Cl.** **125/203.17;** 125/200.16; 125/203.26

[58] **Field of Search** 128/200.14, 200.15, 128/200.16, 200.17, 200.18, 200.19, 200.20, 200.21, 200.22, 200.23, 203.16, 203.17, 203.26

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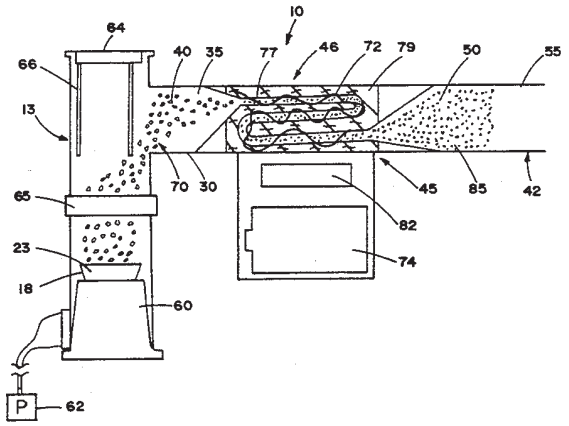
[57] **ABSTRACT**

An aerosol delivery article provides delivery of aerosol particles of relatively small size without the necessity of exposing the material which is aerosolized to a significant degree of heat or high temperatures. An aerosol forming material is a multi-component material comprising an active ingredient and another ingredient having a relatively low vaporization temperature, and preferably that aerosol forming material is in the form of an emulsion. The aerosol forming material is nebulized so as to provide first stage multi-component aerosol particles of fairly large size. The first stage aerosol particles then are subjected to heat so as to vaporize the other ingredient of that aerosol and cause further dispersion of that first stage aerosol. As such, a second stage aerosol composed of fine particles of active ingredient is provided. The heat used to cause the further dispersion of the first stage aerosol is less than that sufficient to cause vaporization, thermal decomposition or undesirable chemical alteration of the active ingredient.

13 Claims, 1 Drawing Sheet



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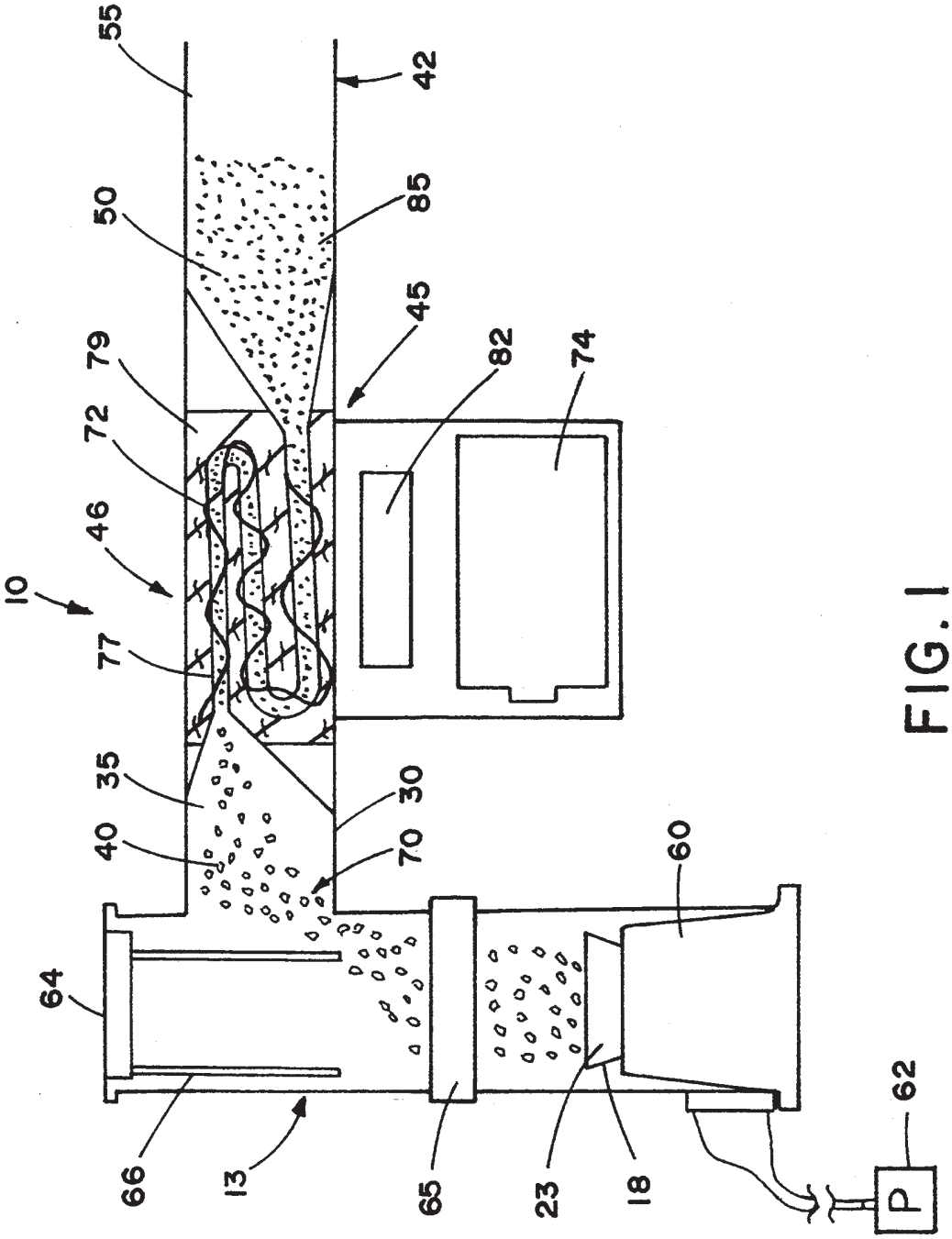

FIG. 1

AEROSOL DELIVERY ARTICLE

BACKGROUND OF THE INVENTION

The present invention relates to aerosol delivery articles, and in particular, to such articles which are capable of providing aerosol particles of relatively small size while subjecting the material to be aerosolized to relatively low temperatures.

It has been desirable to deliver certain medications to a patient in vapor or aerosol form. As such, the patient inhales the medication, and that medication directly enters that patient's respiratory system. See, *Science,* Vol. 260, p. 912 (1993). As a result, there have been efforts towards developing various aerosol delivery devices, principally for the delivery of certain pharmaceutical compositions or drugs. As used herein, the term "drug" includes articles and substances intended for use in the diagnosis, cure, mitigation, treatment or prevention of disease; and other substances and articles referred to in 21 U.S.C. §321(g)(1). Certain aerosol delivery articles and articles for delivering medicaments in vapor form are described in U.S. Pat. No. 1,771,366 to Wyss et al.; U.S. Pat. No. 1,968,509 to Tiffany; U.S. Pat. No. 2,030,075 to Robinson; U.S. Pat. No. 2,057,353 to Whittemore, Jr.; U.S. Pat. No. 3,820,540 to Hirtz et al.; U.S. Pat. No. 4,036,224 to Choporis et al.; U.S. Pat. No. 4,214,146 to Schimanski; U.S. Pat. No. 4,303,083 to Burruss, Jr.; U.S. Pat. No. 4,735,217 to Gerth et al.; U.S. Pat. No. 4,922,901 to Brooks et al.; and U.S. Pat. No. 4,941,483 to Ridings et al.; as well as by Hickey in *Drugs Pharm. Sci.,* Vol. 54, p.255 (1992). Certain other delivery articles are described in U.S. Pat. No. 3,297,029 to Brinkman et al.; U.S. Pat. No. 3,859,398 to Havstad; U.S. Pat. No. 3,864,544 to Van Amerongen; U.S. Pat. No. 3,990,441 to Hoyt et al.; U.S. Pat. No. 4,190,046 to Virag and U.S. Pat. No. 4,523,589 to Krauser.

Certain of the aerosol delivery articles provide medication in aerosol form by mechanical action. In particular, the medication is provided in the form of an aerosol using nebulizers and metered dose inhalers. Such aerosol delivery articles are desirable in that the pharmacological composition to be aerosolized is not subjected to exposure to heat and high temperatures. However, mechanically generated aerosols typically comprise significant numbers of particles of relatively large size (i.e., greater than about 5 μm in diameter). Such large size particles do not always provide the pharmaceutical composition in a form which provides for maximum effectiveness in treating the patient. Aerosol delivery articles which employ heat to evaporate aerosol forming materials which later condense into aerosol particles of relatively small size provide aerosols which are readily inhaled. However, the pharmacological properties of certain pharmaceutical compositions which are aerosolized by vaporization often are undesirably altered, because certain pharmaceutical compositions are quite sensitive to the effects of heat and temperature.

It would be desirable to provide an aerosol delivery article which is capable of producing aerosol particles of relatively small size (e.g., submicron size) without the necessity of subjecting the material to be aerosolized to exposure to a significant degree of heat or high temperatures.

SUMMARY OF THE INVENTION

The present invention relates to an aerosol delivery article. The article includes an aerosol generating means

which is capable of generating an aerosol from a multi-component aerosol forming material. Typically, the aerosol generating means includes a means for mechanically producing aerosol particles from the multi-component material (e.g., a first stage aerosol in the form of a first stage dispersion of aerosol particles). Typically, the multi-component material includes at least one active ingredient to be aerosolized, and at least one other ingredient which provides a capability for causing those first stage aerosol particles to undergo a second stage dispersion or transformation such that aerosol particles of significantly smaller size result. The aerosol delivery article also includes a means for causing the first stage aerosol particles to undergo a second stage dispersion. Typically, the first stage aerosol particles are subjected to heat or other conditions sufficient to destroy the integrity of a significant number of those particles, and hence cause the formation of second stage aerosol particles of relatively small size. Most preferably, the second stage aerosol particles are formed from the active ingredient. The article also includes a delivery means which provides for delivery of the resulting second stage aerosol to the user. Preferably, the aerosol is inhaled by the user into the mouth and/or nose of that user.

In another aspect, the present invention relates to a method for producing an aerosol. A multi-component material capable of forming an aerosol is provided. As such, there is provided an aerosol forming material capable of undergoing a first stage dispersion to form a first aerosol, which first aerosol is capable of undergoing a second stage dispersion to form a second aerosol. The aerosol forming material includes at least one active ingredient and at least one other ingredient capable causing aerosol particles formed from the aerosol forming material to be further dispersed. The aerosol forming material is subjected to conditions sufficient to provide an aerosol from that material. Such conditions typically involve mechanically producing an aerosol from the aerosol forming material, and most preferably involve producing that aerosol under conditions which do not cause the components of that aerosol to experience significant vaporization. The aerosol in the form of a first stage dispersion then is subjected to conditions sufficient to cause a further dispersion of those aerosol particles. Typically, the first stage dispersion is subjected to heat or other conditions sufficient to destroy the integrity of a significant number of those aerosol particles of the first stage dispersion, and hence cause an aerosol in the form of a second stage dispersion of aerosol particles of relatively small size (i.e., of reduced size relative to the first stage aerosol). In such a regard, much of the aerosol of the second stage dispersion can include vapors, gases, and the like. The aerosol so provided then is allowed to pass through a passageway so as to be delivered to the user. As such, an aerosol is delivered into the respiratory system of the user.

BRIEF DESCRIPTION OF THE DRAWINGS

FIG. **1** is a partial sectional view of an aerosol delivery article of the present invention.

DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENTS

Referring to FIG. **1**, aerosol delivery article **10** includes an aerosol generator **13** having a reservoir **18** for an aerosol forming material **23**; an enclosure member **30** for providing a passageway **35** which allows passage of

a first aerosol **40** produced by the aerosol generator through the aerosol delivery article towards mouthend **42** of that article; a heating unit **45**, or other suitable means for providing a heating region **46** thus causing the aerosol particles to undergo further dispersion or a transformation to yield a second aerosol **50**; and a delivery portion **55**, or other suitable means for providing delivery of the second aerosol orally and/or nasally to the user.

The aerosol generator **13** produces a first aerosol **40** from the aerosol forming material **23** contained in the reservoir **18** of that aerosol generator. Typically, the first aerosol **40** is mechanically produced using a nebulizer, or other suitable means for producing an aerosol. A representative nebulizer is available as Microstat Ultrasonic from Mountain Medical Equipment, Inc., Littleton, Colo. Such a nebulizer **13** includes an electrically powered ultrasonic nebulizer head **60** powered by an electrical power source **62**; a valve **64** for inlet of drawn atmospheric air; an inner valve **66** for allowing drawn air to pass near the reservoir **18** containing the aerosol forming material **23**. A connection collar **65** allows the nebulizer to be assembled and disassembled in order to load that nebulizer with aerosol forming material. The inner valve **66** can be adapted to provide for passage of drawn air containing nebulized aerosol forming material (i.e., the first aerosol **40**) out of the aerosol generator through exit passage **70**. As such, the inner valve can include a cyclone region (not shown) so as to provide for a fairly lengthy aerosol passage, and a collection cone (not shown) so as to provide for deposition of overly large size aerosol particles back into the reservoir.

The first aerosol **40** exits the aerosol generator **13** and enters a passageway **35**. As a practical matter, the passageway also can be provided by a region of the aerosol generator. The passageway can vary in terms of its length, cross-sectional dimensions, construction and format. The length of the passageway typically is quite short in order to keep the dimensions of the article small for ease of use and for ease of draw, and in order to avoid loss of aerosol by deposition so that the concentration of the drawn aerosol is not adversely affected. However, the length of the passageway typically is sufficiently long in order that the first aerosol is given sufficient ability to form without being adversely affected by other components of the aerosol delivery article. For example, for the type of aerosol delivery article shown in FIG. **1**, the first aerosol can pass through a passageway of about 5 cm to about 10 cm from the reservoir **18** to the heating unit **45**. As such, it is possible to construct the enclosure member **30** from a material (e.g., a heat resistant plastic material such as a polycarbonate or a polyimide) which is adapted so as to have a smooth inner surface in order to provide for ready transfer of aerosol through the passageway. In addition, it can be desirable to construct the enclosure member **30** from a material which has a low coefficient for thermal conductivity, in order that heat generated by the heating unit **45** does not adversely affect the aerosol generator **13** and the formation of the first aerosol **40**. The enclosure member **30** can have a variety of shapes, such as a generally tubular shape which is shown in FIG. **1**. However, the cross-sectional shape of the enclosure member does not need to be consistent along its length, and can be fruscoconical or helical in shape. Although the cross-sectional area of the passageway can vary, such area typically ranges from about 7 cm^2 to about 10 mm^2.

The enclosure member **30** then includes a heating unit **45**, or other suitable means for causing the first aerosol particles to undergo a further dispersion to yield a second aerosol **50**. The heating unit typically includes a region within the enclosure number **30**, and such a region can be characterized as a heating region **46**. That heating region can have the form of tubes, baffles, or the like. The heating unit provides for a heating region **46** where the first aerosol is heated sufficiently to form the second aerosol, and as such, heat is exchanged between the heating unit and the first aerosol. Exemplary heat exchange units and technology are described in *Perry's Chemical Engineer's Handbook*, Section 11, Sixth Edit. (1984). A case **71** or other means for housing other components of the heating unit **45**, typically is provided outside of the enclosure member **30**. The case **71** provides a convenient and aesthetic holder or chamber for components of the heating unit which are suited to be positioned outside of the enclosure member **30**. Typically, the heating unit generates heat as a result of an electrical resistance heating element **72** and an electrical power source **74**. The power source can be a battery power supply having one or more batteries (as shown in FIG. **1**) or provided by normal household current stepped down by an appropriate transformer. The resistance heating element **72** and vary in terms of size, composition and configuration. For example, the resistance heating element can be provided by graphite yarns, graphite fabrics, Nichrome film or wire, metal screens, metal or ceramic resistance heating materials, or the like. The resistance heating element also can be in thermal contact with a conducting agent **77** (e.g., an aluminum metal sheet) which is configured so as to distribute heat over a desired region of the aerosol delivery article. As shown in FIG. **1**, the resistance heating element **72** is provided by winding a resistance heating wire **72** around a coiled length of metal tubing **77** which acts as a conducting agent for electrically generated heat. It is desirable that the surface temperature of that portion of the heating unit be sufficiently high, the residence time of the aerosol be sufficiently long, and the surface configuration be such to provide a sufficiently high surface area, in order that the aerosol can be adequately heated. The heating region can have the form of a tubular passageway, a coiled passageway, an annular tube, a baffled passageway, passageways having resistance heating screens positioned thereacross, or the like. Typically, the effective length of the passageway of the heating region (i.e., the average distance travelled by the aerosol during heating) is less than about 30 cm, often less than about 25 cm and occasionally less than about 20 cm; but most often is at least about 10 cm. Insulating material **79** (e.g., glass fiber or ceramic fiber) can be positioned within enclosure member **30** so as to surround the tubular conducting agent **77**, and hence ensure that heat generated by resistance heating is efficiently used to heat the aerosol.

The manner in which the heat is provided by the heating unit can vary. Typically, the heating unit includes a current regulating means **82** to control the temperature of the heating element, and representative current regulating means are described in U.S. Pat. No. 4,922,901 to Brooks et al., which is incorporated herein by reference. The current regulating means can be time-based in that a particular current can be passed through a particular resistance heating element for a controlled

period of time in order that a predetermined temperature can be reached and maintained by a time-based on/off switching mechanism which provides sufficient current over controlled intervals of time to maintain a controlled, essentially constant temperature. Current regulating means which modulate current flow through the heating element can be employed in place of on/off time-based circuits. In addition, on/off and current modulating means can be connected to temperature sensors or other sensing means, rather than to a time-based circuit, in order to control the passage of current through the resistance heating element. Such sensors can be temperature sensors such as infrared sensors, piezoelectric films or the like, or thermostats such as bimetallic strips. Such temperature sensors can sense either the temperature of the resistance element directly or the temperature of the aerosol passing the heating element. Alternatively, the temperature sensors can sense the temperature of a second "model" resistance heating element having a heating and cooling character related to that of the resistance heating element. Another type of sensor which can be employed is a dynamic resistance sensor which senses the change in electrical resistance of the heating element during the heating period.

The heating unit can include a switch (not shown) for turning that heating unit on prior to use, and for turning that heating unit off after use. However, the heating unit can be activated an deactivated by a pressure activated switch (not shown); which is actuated to allow current flow and hence heat generation upon draw, and is deactuated to prevent current flow and hence heat generation when draw ceases. A representative pressure actuated switching mechanism and method for operation in a draw controlled aerosol delivery article are set forth in U.S. Pat. No. 4,922,901 to Brooks et al.

The resistance heating element **72**, the electrical power source **74**, the current regulating means **82**, the switching mechanism, and other electronic components of the heating unit **45** are connected together using known techniques by electrically conductive wires (not shown). As such, one skilled in the art of electronics can provide the circuitry capable of producing heat necessary to cause further dispersion of the first stage aerosol particles **40**.

The heat provided by the heating unit acts to alter the character of the first aerosol **40** passing through that region of the aerosol delivery article so as to further disperse that aerosol and form second aerosol **50**. The second aerosol passes through a delivery portion **55** which can be equipped to include a cooling region **85**. The construction and dimensions of the cooling region can vary depending upon factors such as the temperature of the second aerosol upon exiting the heating region, and the desired temperature of that aerosol immediately upon delivery to the user. The cooling region also can allow for condensation of vaporized aerosol forming material into aerosol particles. Typically, the length of the cooling region ranges from about 1 cm to about 5 cm. For example, the cooling region can be constructed so as to provide for sufficient cooling of heated aerosol and thus provide that aerosol at a palatable temperature (i.e., at about 20° C. to about 40° C.).

In use, the user places aerosol forming material **23** into the reservoir **18** of the nebulizer **13**, and provides electrical current (i.e., by using an on/off switch) to power the ultrasonic nebulizer head **60**. Alternatively, for other types of aerosol generators, the aerosol forming material is correspondingly placed into the aerosol generator, and prepared for aerosol generation and delivery. For aerosol forming materials in the form of emulsions which can be characterized as stable, the emulsions can be used as such. However, emulsions which can be characterized as unstable may require agitation prior to use. Meanwhile, the heating unit **45** is turned on so as to generate heat in the heating region of the aerosol delivery article. When the heating unit is capable of generating a sufficient amount of heat, the aerosol delivery article is drawn upon at the extreme mouth end **42**. However, the heating unit also can be draw controlled in order that current is provided to the resistance heating element immediately upon draw and during the draw period. As such, drawn air entering the aerosol generator through valve **64** is used to provide the first aerosol **40** from the aerosol forming material **18**. The first aerosol **40** passes from the aerosol generator **13** through the passageway **35** and is heated in the heating region **46** to provide the second aerosol **50**. The second aerosol then passes into the mouth of the user. As such, the finely dispersed particles of the second aerosol **50** can be drawn into, and hence delivered to, the respiratory system (e.g., the nose and/or mouth, throat, and lungs) of the user. As such, fine particles of the active ingredient can be delivered to the respiratory system of the user.

The aerosol forming material is a multi-component material, and as such, includes at least one active ingredient and at least one other ingredient. The active ingredient can include at least one flavoring agent. The flavoring agent can provide fruit, coffee, tobacco, spice flavor or any other desired flavor, to the aerosol. The flavor can be an artificial flavor or natural flavor (e.g., as provided by fruit or tobacco extracts). Ingredients such as glycerine, triethylene glycol and propylene glycol can be ingredients within the multi-component material. The active ingredient most preferably includes at least one pharmaceutical material.

Pharmaceutical materials useful herein most preferably are those which can be administered in an aerosol form directly into the respiratory system of the user. Typical of such materials are drugs or other types of medicaments which are used in the treatment of asthma, pneumonia, influenza, emphysema, bronchitis, epilepsy, depression, shock, respiratory stress in adults and premature infants, hypertension, Alzheimer's disease, Parkinson's disease, cardiac arrhythmia, sinus congestion, allergies, convulsions, anxiety, schizophrenia, hyperactivity, and the like. Examples of suitable drugs include ephedrine; nicotinic compounds such as nicotine, substituted nicotine compounds and metanicotine; metaproterenol; ritaline; resperine; terbutaline; dopamine; phenytoin; lipid molecules; propranolol; diazepam; diphenhydramine; steroids, including cortico steroids such as cortisone, prednisone, triamcinolone and prednisolone; peptide and polypeptide drugs such as are described in *Science,* Vol. 260, p.912 (1993); synthetic pulmonary surfactants such as dipalmitoyl lecithin; and the like. Representative pharmaceutical materials are set forth in U.S. Pat. No. 5,145,861 to Ducep et al.; U.S. Pat. No. 5,109,010 to Beight et al.; U.S. Pat. No. 5,026,861 to Beight et al.; U.S. Pat. No. 4,999,431 to Cheng et al.; U.S. Pat. No. 4,990,519 to Cheng et al.; U.S. Pat. No. 4,886,811 to Cheng et al.; U.S. Pat. No. 4,861,756 to Jackson; U.S. Pat. No. 4,748,274 to Creege et al.; U.S. Pat. No. 4,650,872 to Wright; U.S. Pat. No. 4,622,422 to Creege; U.S. Pat. No. 4,435,420 to Doherty

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