US006743413B1

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

(10) **Patent No.: US 6,743,413 B1**
(45) **Date of Patent: Jun. 1, 2004**

(54) **SUSPENSION AEROSOL FORMULATIONS**

(75) Inventors: **Robert K. Schultz**, Shoreview, MN (US); **David W. Schultz**, Pine Springs, MN (US); **Martin J. Oliver**, Loughborough (GB); **Robert A. Moris**, Lino Lakes, MN (US); **Philip A. Jinks**, Mount Sorrel (GB)

(73) Assignee: **3M Company**, St. Paul, MN (US)

( * ) 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.: **08/455,280**

(22) Filed: **May 31, 1995**

**Related U.S. Application Data**

(60) Division of application No. 07/878,039, filed on May 4, 1992, which is a continuation-in-part of application No. 07/809,791, filed on Dec. 18, 1991, now abandoned, which is a continuation-in-part of application No. 07/810,401, filed on Dec. 18, 1991, now abandoned.

(51) **Int. Cl.**[7] ..... **A61L 9/04**; A61K 9/00; A01N 25/02

(52) **U.S. Cl.** ..... **424/45**; 424/43

(58) **Field of Search** ..... 424/43–45

(56) **References Cited**

U.S. PATENT DOCUMENTS

| | | | | |
|---|---|---|---|---|
| 2,868,691 | A | 1/1959 | Porush et al. | 167/54 |
| 2,885,427 | A | 5/1959 | Ruh et al. | |
| 3,014,844 | A | 12/1961 | Thiel et al. | 167/82 |
| 3,219,533 | A | 11/1965 | Mullins et al. | |
| 3,261,748 | A | 7/1966 | Larsen et al. | |
| 3,320,125 | A | 5/1967 | Grim et al. | |
| 3,644,353 | A | 2/1972 | Lunts et al. | |
| 3,809,294 | A | 5/1974 | Torgeson | |
| 3,897,779 | A | 8/1975 | Hansen | 128/266 |
| 4,044,126 | A | 8/1977 | Cook et al. | |
| 4,129,603 | A | 12/1978 | Bell | |
| 4,174,295 | A | 11/1979 | Bargigia et al. | |
| 4,241,048 | A | 12/1980 | Durbak et al. | |
| 4,311,863 | A | 1/1982 | Gumprecht | |
| 4,335,121 | A | 6/1982 | Phillipps et al. | |
| 4,347,236 | A | 8/1982 | Tanskanen | |
| 4,352,789 | A | 10/1982 | Thiel | |
| 4,405,598 | A | 9/1983 | Brown | |
| 4,810,488 | A | 3/1989 | Jinks | |
| 4,814,161 | A | 3/1989 | Jinks et al. | 424/45 |
| 4,851,595 | A | 7/1989 | Gumprecht | |
| 4,859,696 | A | 8/1989 | Kamiya | |
| 4,940,171 | A | 7/1990 | Gilroy | |
| 4,945,119 | A | 7/1990 | Smits | |
| 5,118,494 | A | 6/1992 | Schultz | |
| 5,126,123 | A | 6/1992 | Johnson | |
| 5,182,040 | A | 1/1993 | Bartlett | |
| 5,182,097 | A | 1/1993 | Byron et al. | 424/45 |
| 5,190,029 | A | 3/1993 | Byron et al. | 128/200.14 |
| 5,202,110 | A | 4/1993 | Dalby et al. | |
| 5,206,268 | A | 4/1993 | Latter et al. | |
| 5,225,183 | A | 7/1993 | Purewal et al. | |
| 5,230,884 | A | 7/1993 | Evans et al. | |
| 5,254,755 | A | 10/1993 | Li et al. | |
| 5,270,305 | A | 12/1993 | Palmer | |
| 5,290,539 | A | 3/1994 | Marecki | |
| 5,292,499 | A | 3/1994 | Evans et al. | |
| 5,310,762 | A | 5/1994 | Latter et al. | |
| 5,314,682 | A | 5/1994 | Sweval et al. | |
| 5,348,730 | A | 9/1994 | Greenleaf et al. | |
| 5,439,670 | A | 8/1995 | Purewal et al. | 424/45 |
| 5,474,759 | A | 12/1995 | Fassberg et al. | 424/45 |
| 5,492,688 | A | 2/1996 | Byron et al. | 424/45 |
| 5,508,023 | A | 4/1996 | Byron et al. | 424/45 |
| 5,605,674 | A | 2/1997 | Purewal et al. | |

(List continued on next page.)

FOREIGN PATENT DOCUMENTS

| | | | |
|---|---|---|---|
| CA | 2075058 | 3/2001 | |
| DE | 27 03 119 | 8/1977 | |
| DE | 2737132 | 2/1978 | |
| DK | 134923 | 2/1977 | |
| EP | 0 039 369 | 11/1981 | C07J/5/00 |
| EP | 0 379 793 B1 | 1/1990 | |
| EP | 0 365 119 A2 | 4/1990 | |
| EP | 0372777 | 6/1990 | |
| EP | 0384371 | 8/1990 | |
| EP | 0 403 301 B1 | 12/1990 | |
| EP | 0 504 112 A2 | 9/1992 | |
| EP | 0 518 600 | 12/1992 | A61K/9/72 |
| EP | 0 518 601 | 12/1992 | A61K/9/72 |
| EP | 0 656 206 | 6/1995 | |
| EP | 0 656 207 | 6/1995 | |

(List continued on next page.)

OTHER PUBLICATIONS

Letter to European Patent Office, dated Aug. 10, 1995, in corresponding European Application 93901414.8.

Letter to European Patent Office, dated Nov. 17, 1997, in Opposition to EP 553298.

Expert Report of Dr. John J. Sciarra in U.K. Patents Court, Chancery Division, Revocation Proceedings, CH 1997–M–No. 3722/3766, regarding European Patent 0 617 610.

Pumfrey, J., United Kingdom Patent Court decision, dated Jul. 28, 1998, in the High Court of Justice, Chancery Division, Patent Court, combined cases CH 1997 M No. 3766 and CH 1997 M No. 3722 (re European Patent No. 0 617 610).

Jacob , J., United Kingdom Patents Court decision, dated Jun. 30, 1997, in the High Court of Justice, Chancery Division, Patents Court, combined cases CH/96/3771 and CH/96/3773 (re European Patent No. 0,372,777, 0,499,344, and 0,553,298).

Expert Report of Ian Smith dated May 27, 1998, U.K. Patents Court, Chancery Division, Revocation Proceedings, CH 1997–M–No. 3722/3766, regarding European Patent 0 617 610.

(List continued on next page.)

*Primary Examiner*—Thurman K. Page
*Assistant Examiner*—Humera N. Sheikh

(57) **ABSTRACT**

Pharmaceutical suspension aerosol formulations containing a therapeutically effective amount of a drug and HFC 134*a*, HFC 227, or a mixture thereof.

**24 Claims, No Drawings**

U.S. PATENT DOCUMENTS

| | | | | |
|---|---|---|---|---|
| 5,620,631 | A | 4/1997 | Heiskel et al. | |
| 5,653,962 | A | 8/1997 | Akehurst et al. | |
| 5,658,549 | A | 8/1997 | Akehurst et al. | |
| 5,674,471 | A | 10/1997 | Akehurst et al. | |
| 5,674,472 | A | 10/1997 | Akehurst et al. | 424/45 |
| 5,674,473 | A | 10/1997 | Purewal et al. | |
| 5,676,929 | A | 10/1997 | Akehurst et al. | |
| 5,681,545 | A | 10/1997 | Purewal et al. | |
| 5,683,676 | A | 11/1997 | Akehurst et al. | 424/45 |
| 5,683,677 | A | 11/1997 | Purewal et al. | |
| 5,688,782 | A | 11/1997 | Neale et al. | 514/180 |
| 5,695,743 | A | 12/1997 | Purewal et al. | |
| 5,720,940 | A | 2/1998 | Purewal et al. | |
| 5,736,124 | A | 4/1998 | Akehurst et al. | |
| 5,744,123 | A | 4/1998 | Akehurst et al. | |
| 5,766,573 | A | 6/1998 | Purewal et al. | 424/45 |
| 5,776,432 | A | 7/1998 | Schultz | |
| 5,776,434 | A | 7/1998 | Purewal et al. | 424/45 |
| 5,817,293 | A | 10/1998 | Akehurst et al. | 424/45 |
| 5,833,950 | A | 11/1998 | Taylor et al. | 424/45 |
| 5,916,540 | A | 6/1999 | Akehurst et al. | 424/45 |
| 5,922,306 | A | 7/1999 | Akehurst et al. | 424/45 |
| 6,006,745 | A | 12/1999 | Marecki | 128/200.23 |
| 6,013,245 | A | 1/2000 | Taylor et al. | 424/45 |
| 6,200,549 | B1 | 3/2001 | Akehurst et al. | 424/45 |
| 6,221,339 | B1 | 4/2001 | Akehurst et al. | 424/46 |
| 6,238,647 | B1 | 5/2001 | Akehurst et al. | |
| 6,251,368 | B1 | 6/2001 | Akehurst et al. | 424/45 |
| 6,303,103 | B1 | 10/2001 | Akehurst et al. | |
| 6,306,368 | B1 | 10/2001 | Taylor et al. | 424/45 |
| 6,306,369 | B1 | 10/2001 | Akehurst et al. | 424/45 |
| 6,333,023 | B1 | 12/2001 | Akehurst et al. | |
| 6,413,497 | B1 | 7/2002 | Weil et al. | |
| 6,416,743 | B1 | 7/2002 | Fassberg et al. | |
| 6,419,899 | B1 | 7/2002 | Weil et al. | |
| 6,503,482 | B1 | 1/2003 | Fassberg et al. | |
| 2002/0071812 | A1 | 6/2002 | Weil et al. | |

FOREIGN PATENT DOCUMENTS

| | | | |
|---|---|---|---|
| EP | 1 092 430 A1 | 4/2001 | |
| GB | 837465 | 6/1960 | |
| JP | 52-80282 | 5/1977 | |
| SE | 437 766 | 3/1985 | |
| WO | WO 86/03750 | 7/1986 | C07J/5/00 |
| WO | WO 86/04233 | 7/1986 | |
| WO | WO 90/07333 | 7/1990 | |
| WO | WO 90/11754 | 10/1990 | |
| WO | 91/04011 | 4/1991 | |
| WO | 91/11173 | 8/1991 | |
| WO | 91/11495 | 8/1991 | |
| WO | 91/11496 | 8/1991 | |
| WO | 91/14422 | 10/1991 | |
| WO | WO 92/00061 | 1/1992 | |
| WO | 92/00107 | 1/1992 | |
| WO | WO 92/06675 | 4/1992 | |
| WO | 92/08446 | 5/1992 | |
| WO | WO 92/08447 | 5/1992 | |
| WO | WO 92/11190 | 7/1992 | |
| WO | 92/22287 | 12/1992 | |
| WO | 92/22288 | 12/1992 | |
| WO | 93/11743 | 6/1993 | |
| WO | 93/11744 | 6/1993 | |
| WO | WO 93/11745 | 6/1993 | |
| WO | WO 93/11747 | 6/1993 | |
| WO | WP 93/11747 | 6/1993 | |
| WO | WO 94/03153 | 2/1994 | A61K/9/00 |
| WO | WO 98/52542 | 11/1998 | A61K/9/00 |

OTHER PUBLICATIONS

Sanders, Paul A. PhD. *Handbook of Aerosol Technology,* 2nd Edition, 1979 (New York, New York: Van Nostrand Reinhold Company), p 30, 32, 33, 166, 167, 232, 233, 400, 401, 402.

Dalby et al., "CFC Propellant Substitution: P–134a as a Potential Replacement for PL–12 in MDIs", *Pharmaceutical Technology,* Mar. 1990.

Research Disclosure 16265, Oct. 1977.

Research Disclosure 30161, May 1989.

Oberholz, *Frankfuter Allgemenine Zeitung,* Oct. 1989, vol. 25, No. 207, p. 7.

Dalby et al., *Pharmaceutical Technology,* Mar. 1990, vol. 14, No. 3, pp. 26–33.

*Amzacort carton,* William H. Rorer, Inc. Fort Washington, Pennsylvania, USA 19034, 1986.

*Pharmaceutical Journal,* Sep. 29, 1990, vol. 245, pp. 428–429.

*The Theory and Practice of Industrial Pharmacy,* 2nd Ed. 1976 (Philadelphia PA: Lea and Febiger), pp. 270 and 276–278.

*Handbook of Aerosol Technology,* 2nd Edition, 1979 (New York, New York: Van Nostrand Reinhold Company), pp. 30, 32, 33, 166, 167, 232–233.

*U.S. Senate Hearings, May 12–14, 1987,* 343–347, 437 (U.S. Government Printing Office, Washington, D.C., 1987), CIS: 1987–S321–26.

*Hagers Handbook of Pharmaceutical Practice,* 1971, pp. 342–354 (Berlin: Springer–Veriag).

Gennaro, A.R. 91985). *Remington's Pharmaceutical Sciences,* 17th Ed., Mack Pub. Co., pp. 1670–1677.

Transcript of Judgment by Mr. Justice Pumfrey.

Graepel, P. and Alexander, D. J., Journal of Aerosol Medicine, vol. 4, No. 3, 1991.

Oberholz, 1989, Frankfuter Allgemenine Zeitung, 25:207:7.

Dalby et al., 1990, Pharmaceutical Technology, 14:3:26–33.

Amzacort carton, 1986, William H. Rorer, Inc., Fort Washington, Pennsylvania, USA 19034.

1990, Pharmaceutical Journal, (Sep. 29) 245:428–429.

1976, The Theory and Practice of Industrial Pharmacy, 2nd Ed., (Philadelphia, PA, Lea and Febiger), pp. 270 and 276–678.

1979, Handbook of Aerosol Technology, 2nd Ed., (New York, New York: Van Nostrand Reinhold Company), pp. 30, 32, 33, 166, 167, 232–233.

U.S. Senate Hearings, May 12–14, 1987, 343–347, 437 (U.S. Government Printing Office, Washington, D.C., 1987), CIS: 1987–S321–26.

1971, Hagers Handbook of Pharmaceutical Practice, pp. 342–354 (Berlin: Springer–Veriag).

Genarro, A. R., 1985, Remington's Pharmaceutical Sciences, 17th Ed., Mack Pub. Co., pp. 1670–1677.

"CFC–Free Aerosols—The Final Hurdle", Manufacturing Chemist, 63(7):22–23, 1992.

Kontny et al., "Issues Surrounding MDI Formulation Development with Non–CFC Propellants", Journal of Aerosol Medicine, 4(3):181–187, 1991.

Moren, F., "Chlorofluorocarbons (CFCs) and Their Replacement", The Regulatory Affairs Journal, Jun. 1991, pp. 385–389.

Dalby, R., "Special Considerations in the Formulation of Suspension Type Metered Dose Inhalers", Aerosol Age, pp. 22–24, 26–28, 34, and 89, Oct. 1990.

Byron, Respiratory Drug Delivery, CRC Press, Inc., FL, pp. 168–201, 1990.
Martindale: The Extra Pharmacopoeia. 28th Edition. Edited by James E.F. Reynolds, Assistant Editor Anne B. Prasad. The Pharmaceutical Press: London, 1982. Entry No. 1068–t.
The Merck Index (Budavari, Susan, Editor, Merck & Co., Inc. U.S.A. 1989).
J. A. Ranucci et al., "Controlled Flocculation in Metered'Dose Aerosol Suspensions" *Pharmaceutical Technology,* pp. 69–74, Apr. 1990.

# SUSPENSION AEROSOL FORMULATIONS

This is a division of application Ser. No. 07/878,039 filed May 4, 1992, now abandoned.

This application is a continuation-in-part of commonly assigned, copending applications U.S. Ser. No. 07/809,791 and U.S. Ser. No. 07/810,401, now abandoned both filed Dec. 18, 1991, and both incorporated herein by reference.

## BACKGROUND OF THE INVENTION

1. Field of the Invention

This invention relates to pharmaceutical aerosol formulations. In another aspect this invention relates to pharmaceutical suspension aerosol formulations wherein the propellant comprises HFC 134a or HFC 227. In another aspect, it relates to pharmaceutical suspension aerosol formulations containing pirbuterol. In another aspect, it relates to pharmaceutical suspension aerosol formulations containing albuterol sulfate.

2. Description of the Related Art

Pharmaceutical suspension aerosol formulations currently use a mixture of liquid chlorofluorocarbons as the propellant. Fluorotrichloromethane, dichlorodifluoromethane and dichlorotetrafluoroethane are the most commonly used propellants in aerosol formulations for administration by inhalation.

Chlorofluorocarbons (CFCs), however, have been implicated in the destruction of the ozone layer and their production is being phased out.

Hydrofluorocarbon 134a (HFC 134a, 1,1,1,2-tetrafluoroethane) and hydrofluorocarbon 227 (HFC 227, 1,1,1,2,3,3,3-heptafluoropropane) are viewed as being more ozone friendly than many chlorofluorocarbon propellants; furthermore, they have low toxicity and vapor pressures suitable for use in aerosols.

Patent Applications WO 91/11495 and WO 91/11496 (both by Weil) describe pharmaceutical suspension aerosol formulations comprising a medicinal agent, optionally a surfactant, and a propellant mixture containing 1,1,1,2,3,3,3-heptafluoropropane and one or more additional components, e.g., pentane, butane, propellant 134a, propellant 11, propellant 125, or propellant 152a.

European Patent Office Publication 0 384 371 (Heiskel) describes solution aerosols in which 1,1,1,2,3,3,3-heptafluoropropane or its mixture with propane, butane, isobutane, dimethyl ether, or 1,1-difluoroethane serves as the propellant. The application does not, however, disclose suspension aerosols or pharmaceutical aerosol formulations.

European Patent Application 89.312270.5 (Purewal et al.) discloses, inter alia, aerosol formulations comprising a medicament, 1,1,1,2-tetrafluoroethane, a surface active agent, and at least one compound having higher polarity than 1,1,1,2-tetrafluoroethane.

U.S. Pat. No. 2,868,691 (Porush et al.) discloses aerosol formulations comprising a medicament, a halogenated lower alkane propellant, and a cosolvent which assists in dissolving the medicament in the propellant. The chemical formula for the propellant given in Col. 2, lines 6–16, generically embraces HFC 134a and HFC 227. Examples of cosolvents disclosed include ethanol and diethyl ether.

U.S. Pat. No. 3,014,844 (Thiel et al.) discloses aerosol formulations comprising a micronized medicament, a halogenated lower alkane propellant and a surface-active agent to assist in the suspension of the medicament in the propellant. The chemical formula for the propellant given in Col. 4, lines 17–28, generically embraces HFC 134a and HFC 227.



Patent Application WO 90/01454 (Greenleaf et al.) discloses aerosol compositions having HFC 134a as the propellant and comprising a medicament coated with a non-perfluorinated surface active dispersing agent. This application describes control formulations containing only HFC 134a and 0.866 percent by weight of a drug.

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) 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.

Pirbuterol acetate is a relatively selective beta-2 adrenergic bronchodilator. MAXAIR™ Inhaler (commercially available from 3M Pharmaceuticals, St. Paul, Minn) is a metered dose aerosol unit containing a fine-particle suspension of pirbuterol acetate in the propellant mixture of trichloromonofluoromethane and dichlorodifluoromethane, with sorbitan trioleate.

## SUMMARY OF THE INVENTION

This invention provides a pharmaceutical suspension formulation suitable for aerosol administration, consisting essentially of a therapeutically effective amount of a drug and a propellant selected from the group consisting of HFC 134a, HFC 227, and a mixture thereof, said formulation being further characterized in that it exhibits substantially no growth in particle size or change in crystal morphology of the drug over a prolonged period, is substantially and readily redispersible, and upon redispersion does not flocculate so quickly as to prevent reproducible dosing of the drug.

This invention also provides an aerosol canister containing a formulation as described above in an amount sufficient to provide a plurality of therapeutically effective doses of the drug. Also provided is a method of preparing a formulation as described above, comprising the steps of: (i) combining an amount of the drug sufficient to provide a plurality of therapeutically effective doses and a propellant selected from the group consisting of HFC 134a, HFC 227, and a mixture thereof, in an amount sufficient to propel from an aerosol canister a plurality of therapeutically effective doses of the drug; and (ii) dispersing the drug in the propellant. This invention further provides a method of treating a mammal having a condition capable of treatment by inhalation, comprising the step of administering by inhalation a formulation as described above to the mammal.

In another aspect, this invention provides suspension aerosol formulations comprising a therapeutically effective amount of micronized albuterol sulfate and HFC 227 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 HFC 227 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 HFC 227 as substantially the only propellant.

In another aspect this invention provides suspension aerosol formulations comprising a therapeutically effective amount of micronized pirbuterol acetate and a propellant comprising HFC 227, the formulation being further characterized in that it is substantially free of perfluorinated surfactant. This invention also provides suspension aerosol formulations comprising a therapeutically effective amount of micronized pirbuterol acetate, about 0.1 to about 12 percent by weight of ethanol, and a propellant comprising HFC 227. This invention also provides suspension aerosol formulations comprising a therapeutically effective amount of micronized pirbuterol acetate, about 5 to about 12 percent by weight of ethanol, about 0.05 to about 0.5 percent by weight of oleic acid, and a propellant comprising HFC 227.

This invention also provides a method for inducing bronchodilation in a mammal, comprising administering to the mammal a formulation as described above by inhalation.

## DETAILED DESCRIPTION OF THE INVENTION

The term "suspension aerosol formulation" as used herein refers to a formulation in which the drug is in particulate form and is substantially insoluble in the propellant.

Amounts expressed herein in terms of percent refer to percent by weight based on the total weight of the formulation.

The formulations of the invention that consist essentially of drug and a propellant contain drug and propellant in relative amounts such that a formulation suitable for aerosol administration is obtained without the need for additional components. Such formulations preferably contain less than an effective stabilizing amount of surfactant and more preferably are substantially free of surfactant and other components.

The formulations of the invention contain a drug in a therapeutically effective amount, that is, an amount such that the drug can be administered as an aerosol (e.g., topically or by oral or nasal inhalation) and cause its desired therapeutic effect with one dose, or less preferably several doses, from a conventional valve, e.g., a metered dose valve. "Amount" as used herein refers to quantity or to concentration as appropriate to the context. The amount of a drug that constitutes a therapeutically effective amount varies according to factors such as the potency, efficacy, and the like, of the particular drug, on the route of administration of the formulation, and on the device used to administer the formulation. A therapeutically effective amount of a particular drug can be selected by those of ordinary skill in the art with due consideration of such factors. Particularly in formulations of the invention intended for oral inhalation into the lungs, the drug is preferably micronized, i.e., about 90 percent or more of the particles have a diameter of less than about 10 microns, in order to assure that the particles can be inhaled into the lungs.

The particular amount of drug that will remain suspended in a formulation of the invention for a time sufficient to allow reproducible dosing of the drug depends to some extent on the nature of the particular drug, e.g., its density, and on the particular propellant used in the formulation. Generally, however, it has been found that when drug concentrations of less than about 0.1 percent are used in a formulation of the invention the drug flocculates to some degree but generally does not settle or cream to the extent that the suspension becomes unsuitable for use as an aerosol formulation, e.g., in a metered dose inhaler. Therefore as regards drug concentration such formulations are acceptably homogeneous.

When drug concentrations greater than about 0.1 percent but less than about 0.5 percent are used in a formulation of the invention it is sometimes seen that the drug flocculates considerably in the formulation and therefore might have an increased tendency to cream or settle. As discussed below in connection with the propellant component of the formulations of the invention, in these instances it is preferable to select the propellant in a manner that minimizes creaming and settling of the drug in order to assure that the formulation is acceptably homogeneous as regards drug concentration.

As drug concentration increases, e.g., beyond about 0.5 percent, the tendency of the drug to flocculate generally increases also. However, the volume occupied by the flocculated drug also increases and the flocculated drug begins to occupy substantially all of the volume of the formulation. In such instances the flocculated drug often shows a lesser tendency to cream or settle. As regards drug concentration such formulations are acceptably homogeneous.

Generally the concentration of the drug in a formulation of the invention is preferably less than about 0.1 percent, more preferably less than about 0.08 percent, and most preferably less than about 0.05 percent. Accordingly, it is preferred according to this invention that the drug have a potency such that concentrations less than about 0.1 percent, more preferably less than about 0.08 percent, and most preferably less than about 0.05 percent, are therapeutically effective. Preferred drugs for use in the formulations of the invention therefore include formoterol, salmeterol, and pharmaceutically acceptable salts thereof, particularly formoterol fumarate. Other drugs that can be formulated according to this invention include albuterol, beclomethasone dipropionate, cromolyn, pirbuterol, and pharmaceutically acceptable salts and solvates thereof, particularly albuterol sulfate, disodium cromoglycate, and pirbuterol acetate.

The propellant in a formulation of the invention can be HFC 134a, HFC 227, or a mixture thereof in any proportion. The propellant is present in an amount sufficient to propel a plurality of doses from a metered dose inhaler. The density of HFC 134a differs from the density of HFC 227. Therefore the density of the propellant can be adjusted within limits by using mixtures of HFC 134a and HFC 227 in order to accommodate the density of the drug. It is sometimes preferred that the propellant be selected such that the propellant density is as closely matched as possible to the drug density in order to minimize tendencies for the drug to settle or cream, particularly when drug concentration is greater than 0.1 percent or when the drug concentration is between about 0.1 percent and about 0.5 percent.

The pirbuterol acetate formulations of the invention contain a therapeutically effective amount of pirbuterol acetate. Preferably, the pirbuterol acetate constitutes about 0.4 to about 1.0 percent by weight, more preferably about 0.45 to about 0.9 percent by weight, of the aerosol formulation. Preferably the pirbuterol acetate is micronized.

Ethanol can optionally be included in a pirbuterol acetate aerosol formulation of the invention. When ethanol is present it constitutes from about 0.1 to about 12 percent by weight, preferably from about 5 to about 12 percent by weight of the aerosol formulation. In another aspect of this

DOCKET ALARM

# Explore Litigation Insights

Docket Alarm provides insights to develop a more informed litigation strategy and the peace of mind of knowing you're on top of things.

## Real-Time Litigation Alerts

Keep your litigation team up-to-date with **real-time alerts** and advanced team management tools built for the enterprise, all while greatly reducing PACER spend.

Our comprehensive service means we can handle Federal, State, and Administrative courts across the country.

## Advanced Docket Research

With over 230 million records, Docket Alarm's cloud-native docket research platform finds what other services can't. Coverage includes Federal, State, plus PTAB, TTAB, ITC and NLRB decisions, all in one place.

Identify arguments that have been successful in the past with full text, pinpoint searching. Link to case law cited within any court document via Fastcase.

## Analytics At Your Fingertips

Learn what happened the last time a particular judge, opposing counsel or company faced cases similar to yours.

Advanced out-of-the-box PTAB and TTAB analytics are always at your fingertips.

## API

Docket Alarm offers a powerful API (application programming interface) to developers that want to integrate case filings into their apps.

**LAW FIRMS**
Build custom dashboards for your attorneys and clients with live data direct from the court.

Automate many repetitive legal tasks like conflict checks, document management, and marketing.

**FINANCIAL INSTITUTIONS**
Litigation and bankruptcy checks for companies and debtors.

**E-DISCOVERY AND LEGAL VENDORS**
Sync your system to PACER to automate legal marketing.