Abstract:

Compositions containing tiotropium or a pharmaceutically acceptable salt or solvate thereof, citric acid or a salt thereof, glycerol, ethanol, and a propellant, as well as aerosol canisters and inhalers containing the same. Methods of manufacturing and using the compositions, aerosol canisters, and inhalers.
FORMULATION AND AEROSOL CANISTERS, INHALERS, AND THE LIKE CONTAINING THE FORMULATION

TECHNICAL FIELD

The present disclosure relates to formulations used for, as an example, an inhaled dosage form, as well as aerosol canisters, inhalers, metered dose inhalers, and the like containing the same.

BACKGROUND

Tiotropium compositions are known in the art. Such compositions are not necessarily acceptable, for example, such compositions may not be acceptable for use in inhalers. Further, such formulations are not necessarily solution formulations.

SUMMARY

Compositions can comprise tiotropium or a pharmaceutically acceptable salt or solvate thereof in a concentration of 0.0075 wt% to 0.015 wt% based on the weight of tiotropium bromide; citric acid or a salt thereof in a concentration greater than 0.10 wt% and no greater than 0.2 wt% based on the weight of free citric acid; glycerol in a concentration of 0.5 wt% to 2.0 wt%; ethanol in a concentration of up to 20 wt%; and a propellant consisting essentially of 1,1,1,2-tetrafluoroethane. Aerosol canisters can comprise such compositions, which can be under pressure greater than atmospheric pressure in the aerosol canisters. Inhalers can comprise such aerosol canisters.

DETAILED DESCRIPTION

Throughout this disclosure, singular forms such as "a," "an," and "the" are often used for convenience; however, it should be understood that the singular forms are meant to include the plural unless the singular alone is explicitly specified or is clearly indicated by the context.

Some terms used in this application have special meanings, as defined herein. All other terms will be known to the skilled artisan, and are to be afforded the meaning that a person of skill in the art at the time of the invention would have given them.

Elements in this specification that are referred to as "common," "commonly used," and the like, should be understood to be common within the context of the compositions, articles, such as inhalers and metered dose inhalers, and methods of this disclosure; this terminology is not used to mean that these features are present, much less common, in the prior art. Unless otherwise specified, only the Background section of this Application refers to the prior art.

The "particle size" of a single particle is the size of the smallest hypothetical hollow sphere that could encapsulate the particle.
The "mass median diameter" of a plurality of particles refers to the value for a particle diameter at which 50% of the mass of particles in the plurality of particles have a particle size smaller than the value and 50% of the mass of particles in the plurality of particles have a particle size greater than the value.

The "ex-actuator size" of a plurality of particles refers to the mass median aerodynamic diameter (sometimes abbreviated as "MMAD") of the plurality of particles after the plurality of particles has passed through the actuator of an inhaler, such as a metered dose inhaler, as measured by the procedure described in the United States Pharmacopeia <601>.

"Weight percent" or "percent by weight," when describing the amount of component in a composition refers to percent weight of the component based on the weight of the entire composition. Weight percent is sometimes abbreviated "wt. %.

"Fine particle dose" is determined according 2015 United States Pharmacopia test <601>.

"Fine Particle Mass," often abbreviated "FPM," is in this disclosure determined mathematically using Copley Inhaler Testing Data Analysis Software (CITDAS) (Copley Scientific LTD., Nottingham, United Kingdom).

"Fine Particle Fraction," often abbreviated "FPF," is determined according to 2015 United States Pharmacopia test <601> and is calculated as [FPM / (sum of sample content for throat assembly, cups 1-7, MOC, and the filter)] x 100.

A component is said to be present in amounts "up to" a reference amount or concentration when the component is not absent but is present in an amount no greater than the reference amount or concentration. Thus, a component present "up to" an amount or concentration does not include the case where the component is absent or present in 0% concentration.

When the concentration of tiotropium is discussed in this disclosure, for convenience it is referred to in terms of the concentration of tiotropium bromide, unless the disclosure specifically refers to the salt form. It should therefore be understood that if another form or salt of tiotropium is used, the concentration of that other form or salt should be calculated on a basis relative to tiotropium bromide. A person of ordinary skill in the relevant arts can easily perform this calculation by comparing the molecular weight of the form or salt of tiotropium that is used to the molecular weight of tiotropium bromide.

Formulation

The formulation can be a solution. Solution formulations, especially for use in aerosols, can have several advantages over suspension formulations. Such advantages include being homogeneous so that users do not need to agitate the formulation to ensure a correct dose. Also, because they are homogeneous, solution formulations provide essentially identical amounts of drug per mass of dose for each dose in an inhaler, whereas inhomogeneous suspensions may lack this consistency.

The pharmaceutical formulation can comprise tiotropium. Tiotropium is a cationic material, and is therefore typically in the form of one or more physiologically acceptable salts or solvates.
Tiotropium bromide is most common. In many cases, the tiotropium bromide is anhydrous tiotropium bromide.

Any suitable concentration of tiotropium can be used. When the concentration of tiotropium is expressed in terms of mg/mL of tiotropium bromide, then the concentration of tiotropium can be no more than 0.15 mg/mL, no more than 0.14 mg/mL, no more than 0.13 mg/mL, no more than 0.12 mg/mL, no more than 0.11 mg/mL, no more than 0.10 mg/mL, no more than 0.09 mg/mL, no more than 0.08 mg/mL, no more than 0.07 mg/mL, no more than 0.06 mg/mL, or no more than 0.05 mg/mL. The concentration of tiotropium, again expressed in terms of tiotropium bromide, can be no less than 0.05 mg/mL, no less than 0.06 mg/mL, no less than 0.07 mg/mL, no less than 0.08 mg/mL, no less than 0.09, no less than 0.1 mg/mL, no less than 0.11 mg/mL, no less than 0.12 mg/mL, or no less than 0.13 mg/mL. Particular embodiments use tiotropium in an amount of about 0.08 mg/mL to about 0.12 mg/mL, such as 0.08 mg/mL to 0.12 mg/mL, about 0.09 mg/mL to about 0.11 mg/mL, such as 0.09 mg/mL to 0.11 mg/mL, about 0.1 mg/mL, or in some cases 0.1 mg/mL. When the tiotropium is in the form of tiotropium bromide, 0.1 mg/mL corresponds to 0.1204 mg/mL tiotropium bromide. When expressed in terms of wt%, the concentration of tiotropium (in terms of tiotropium bromide) is often no greater than 0.15, no greater than 0.14, no greater than 0.0125, or no greater than 0.012. When expressed in terms of wt%, the concentration of tiotropium (in terms of tiotropium bromide) is often no less than 0.005, no less than 0.006, no less than 0.0075, no less than 0.008, or no less than 0.01.

The ex-actuator size of the tiotropium particles, such as tiotropium bromide particles, can be any suitable ex-actuator size. Exemplary suitable ex-actuator sizes can be no less than 1 micrometer, no less than 1.5 micrometers, no less than 2 micrometers, no less than 2.5 micrometers, no less than 3 micrometers, or no less than 3.5 micrometers. Exemplary suitable ex-actuator sizes can also be no greater than 5.0 micrometers, no greater than 4.5 micrometers, no greater than 4.0 micrometers, no greater than 3.5 micrometers, no greater than 3.0 micrometers, no greater than 2.5 micrometers, no greater than 2.0 micrometers, or no greater than 1.5 micrometers. 2.5 micrometer to 3.5 micrometers is common.

The tiotropium particles, such as tiotropium bromide particles, produced by the inhaler can also be characterized by the mass of their fine particle dose. The mass of the fine particle dose, in micrograms, is typically no more than 4, no more than 3.5, no more than 3, no more than 2, such as no more than 1.9, no more than 1.8, no more than 1.7, no more than 1.6, or no more than 1.5. The mass of the fine particle dose is also typically no less than 0.5, such as no less than 0.6, no less than 0.7, or no less than 0.8.

The tiotropium can be present in any suitable concentration in the formulation. The concentration is often expressed in terms of tiotropium bromide; if a different tiotropium salt is used, a person of ordinary skill in the art is able to calculate the concentration of the particular tiotropium salt used in terms of tiotropium bromide using the ratio of the molar mass of the tiotropium salt being used to the molar mass of tiotropium bromide.
A propellant can also be included in the formulation. The prior art recognizes two common propellants for aerosol formulations: HFA 134a and HFA-227. In the prior art, those two propellants are often deemed to be equivalent. Surprisingly, for the specific formulations disclosed in this Application, solutions cannot be formed if the propellant is HFA-227. In order to form solutions, the propellant must consist essentially of HFA-134a (also known as 1,1,1,2-tetrafluoroethane). In this context, “consisting essentially of” means that there is sufficient HFA-134a to create a solution formulation; minor, insubstantial, or trace amounts of other propellants, such as HFA-227, can be present so long as those amounts are insufficient to cause the components to either not form a solution or to cause one or more components of the solution to precipitate after the solution is formed. The inventors prepared several tiotropium compositions that are analogous to those described herein but use HFA-227 instead of HFA-134a, and none of the HFA-227 compositions formed solutions that were stable upon storage; most HFA-227 compositions did not form solutions at all. Thus, the HFA-134a content of the propellant on a weight percent basis is typically at least 90%, such as at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97% at least 98%, at least 99%, at least 99.25%, at least 99.5%, or at least 99.75%. In some cases the propellant comprises 1,1,1,2-tetrafluoroethane.

On a weight percent basis, the amount of propellant in the formulation is typically at least 78% or at least 83%. In many cases, the propellant is 82 to 85 percent by weight, or 83 to 85 percent by weight of the formulation.

Ethanol is used to ensure adequate concentration of drug can be dissolved in the propellant system. On a weight percent basis, the amount of ethanol used, if any, is typically no greater than 20, no greater than 19, no greater than 18, no greater than 17, no greater than 16, no greater than 15.5, no greater than 15, no greater than 14.5, no greater than 14, no greater than 13, no greater than 12, no greater than 11, or no greater than 10. The amount of ethanol used can also be, on a weight percent basis, no less than 10, no less than 11, no less than 12, no less than 13, no less than 14, no less than 14.5, no less than 15, no less than 15.5, no less than 16, no less than 17 or no less than 18. In many cases, the ethanol is about 13 to about 17 percent by weight, 13 to 17 percent by weight, such as about 14 to about 16 percent by weight, 14 to 16 percent by weight, about 14.5 to about 15.5 percent by weight, 14.5 to 15.5 percent by weight, or, in one particular case, about 15 percent by weight or more particularly 15 percent by weight. Even with the addition of ethanol a solution of adequate concentration of tiotropium has not been made with HFA-227 as the propellant. Formulations that were attempted with a large amounts of HF-227 propellant did not form solutions.

In many cases, the combined amount of propellant and ethanol in the formulation, on a weight percent basis, is at least 95 percent, at least 97 percent, at least 98 percent, at least 99 percent, at least 99.5 percent, or at least 99.7 percent.

One or more ex-actuator size affecting compound may be included. Ex-actuator size affecting compounds can change the size of the drug particles as measured after actuation of an inhaler, such as
a metered dose inhaler, containing the composition. Surfactants can be used for this purpose. Most pharmaceutically acceptable surfactants are suitable for use with an inhaler. Typical surfactants include oleic acid, sorbitan monooleate, sorbitan trioleate, soya lecithin, polyethylene glycol, polyvinylpyrrolidone, or combinations thereof. Oleic acid, polyvinylpyrrolidone, or a combination thereof is most common. A combination of polyvinylpyrrolidone and polyethylene glycol is also commonly employed. When polyvinylpyrrolidone is employed, it can have any suitable molecular weight. Examples of suitable weight average molecular weights are from 10 to 100 kilodaltons, typically from 10 to 50, 10 to 40, 10 to 30 or 10 to 20 kilodaltons. When polyethylene glycol is employed, it can be any suitable grade. PEG 100 and PEG 300 are most commonly employed. Most commonly, however, the ex-actuator size affecting compound is glycerol. Alternatively, the one or more ex-actuator size affecting compound may be excluded.

When used, the ex-actuator size affecting compound, particularly glycerol, can be present in a weight percent basis of no more than 2.0%, no more than 1.9%, no more than 1.8%, no more than 1.7%, no more than 1.6%, no more than 1.55%, no more than 1.5%, no more than 1.45%, no more than 1.4%, no more than 1.3%, no more than 1.2%, no more than 1.1%, no more than 1.0%, no more than 0.9%, no more than 0.8%, or no more than 0.75%. The ex-actuator size affecting compound, particularly glycerol, can be present in a weight percent basis of no less than 1.0%, no less than 1.1%, no less than 1.2%, no less than 1.3%, no less than 1.4%, no less than 1.45%, no less than 1.5%, no less than 1.55%, no less than 1.6%, no less than 1.7%, no less than 1.8%, or no less than 1.9%. Thus, the ex-actuator size affecting compound, particularly glycerol, can be present, on a weight percent basis, in about 0.7% to about 1.7%, 0.7% to 1.7%, about 0.8% to 1.6%, 0.8% to 1.6%, about 0.9% to about 1.6%, 0.9% to 1.6%, about 1.0% to about 1.5%, or 1.0% to 1.5%. Particular examples use either 1.0% or 1.5%.

One or more stabilizing agents can be included. The one or more stabilizing agents can be any agent that increases the stability of the formulation. The stabilizing agents can be, for example, antioxidants such as sacrificial antioxidants. Any pharmaceutically acceptable stabilizing agent can be used. On particular stabilizing agent is citric acid or a salt thereof.

When employed, citric acid or the salt thereof can be present, on a weight percent basis, in amounts of no less than 0.075%, no less than 0.08%, no less than 0.09%, no less than 0.10%, no less than 0.11%, no less than 0.12%, no less than 0.13%, no less than 0.14%, no less than 0.15%, no less than 0.16%, no less than 0.17%, no less than 0.18%, no less than 0.19%, or no less than 0.20%. The citric acid can be present, on a weight percent basis, in amounts of no more than 0.20%, 0.19%, 0.18%, 0.17%, 0.16%, 0.15%, 0.14%, 0.13%, 0.12%, 0.11%, 0.1%, or 0.09%. Exemplary amounts of citric acid, on a weight percent basis, are about 0.12% to about 0.18%, 0.12% to 0.18%, about 0.13% to about 0.17%, 0.13% to 0.17%, about 0.14% to about 0.16%, 0.14% to 0.16%, about 0.15%, or 0.15%. When a salt of citric acid is used, the weight percent values in this paragraph should be
understood to be based on the weight of free citric acid (i.e., without considering the weight of the
cation). Most commonly, citric acid alone is used.

The formulations as described herein can be particularly advantageous because they can stabilize
the tiotropium, such as tiotropium bromide, contained therein. Stability of the formulation can be
measured by analyzing change in fine particle fraction over time.

Inhaler

Any of the above-described formulations can be used with any type of inhaler. Metered dose
inhalers are most common. When the inhaler is a metered dose inhaler, any metered dose inhaler can
be employed. Suitable metered dose inhalers are known in the art.

For example, the above-described formulations can be present in a canister, such as a sealed
canister. Such sealed canister can contain any of the above-described formulations under pressure,
particularly under a pressure greater than ambient atmospheric pressure.

Typical metered dose inhalers for the pharmaceutical formulations described herein contain an
aerosol canister fitted with a valve. The canister can have any suitable volume. The brimful capacity
canister will depend on the volume of the formulation that is used to fill the canister. In typical
applications, the canister will have a volume from 5 mL to 500 mL, such as, for example 10 mL to
500 mL, 25 mL to 400 mL, 5 mL to 50 mL, 8 mL to 30 mL, 10 mL to 25 mL, or 50 to 250 mL. The
canister will often have sufficient volume to contain enough medicament for delivering an appropriate
number of doses. The appropriate number of doses is discussed herein. The valve is typically
affixed, or crimped, onto the canister by way of a cap or ferrule. The cap or ferrule is often made of
aluminum or an aluminum alloy, which is typically part of the valve assembly. One or more seals can
be located between the canister and the ferrule. The seals can be one or more of O-ring seals, gasket
seals, and the like. The valve is typically a metered dose valve. Typical valve sizes range from 20
microliters to 100 microliters. Specific valve size that are commonly employed include 25, 50, 60,
and 63 microliter valve sizes.

The container and valve typically include an actuator. Most actuators have a patient port, which
is typically a mouthpiece, for delivering the formulation contained in the canister. The patient port
can be configured in a variety of ways depending on the intended destination of the formulation. For
example, a patient port designed for administration to the nasal cavities will generally have an upward
slope to direct the formulation to the nose. The actuator is most commonly made out of a plastic
material. Typical plastic materials for this purpose include at least one of polyethylene and
polypropylene. Typical MDIs have an actuator with a nozzle. In use, the aerosol spray can emerge
from this nozzle before exiting the mouthpiece of the actuator. The nozzle can be characterized by an
orifice diameter and a jet length. Any suitable orifice diameter can be used. Typical orifice diameters
are from 0.2 mm to 0.65 mm, with 0.2 mm to 0.4 mm being particularly useful for delivery of solution
formulations, such as the solution formulations discussed herein. Typical orifice jet length is from 0.5 mm to 1 mm. Specific examples include orifice diameters of 0.25 mm, 0.3 mm, or 0.4 mm, any of which can have a jet length of 0.8 mm.

A metered dose valve is typically present, and is often located at least partially within the canister and at least partially in communication with the actuator. Typical metered dose valves include a metering chamber that is at least partially defined by an inner valve body through which a valve stem passes. The valve stem can be biased outwardly by a compression spring to be in a sliding sealing engagement with an inner tank seal and outer diaphragm seal. The valve can also include a second valve body in the form of a bottle emptier. The inner valve body, which is sometimes referred to as the primary valve body, defines, in part, the metering chamber. The second valve body, which is sometimes referred to as the secondary valve body, defines, in part, a pre-metering region (sometimes called a pre-metering chamber) in addition to serving as a bottle emptier. The outer walls of the portion of the metered dose valve that are located within the canister, as well as the inner walls of the canister, define a formulation chamber for containing the pharmaceutical formulation.

In use, the pharmaceutical formulation can pass from the formulation chamber into the metering chamber. In moving to the metering chamber, the formulation can pass into the above-mentioned pre-metering chamber through an annular space between the secondary valve body (or a flange of the secondary valve body) and the primary valve body. Pressing the valve stem towards the interior of the container actuates the valve, which allows the pharmaceutical formulation to pass from the pre-metering chamber through a side hole in the valve stem, through an outlet in the valve stem, to an actuator nozzle, and finally through the patient port to the patient. When the valve stem is released, the pharmaceutical formulation enters the valve, typically to the pre-metering chamber, through an annular space and then travels to the metering chamber.

The pharmaceutical formulation can be placed into the canister by any known method. The two most common methods are cold filling and pressure filling. In a cold filling process, the pharmaceutical formulation is chilled to an appropriate temperature, which is typically -50°C to -60°C C for formulations that use propellant HFA 134a, HFA 227, or a combination thereof, and added to the canister. The metered dose valve is subsequently crimped onto the canister. When the canister warms to ambient temperature, the vapor pressure associated with the pharmaceutical formulation increases thereby providing an appropriate pressure within the canister.

In a pressure filling method, the metered dose valve can be first crimped onto the empty canister. Subsequently, the formulation can be added through the valve into the container by way of applied pressure. Alternatively, all of the non-volatile components can be first added to the empty canister before crimping the valve onto the canister. The propellant can then be added through the valve into the canister by way of applied pressure.
The total dose of tiotropium, such as tiotropium bromide or more particularly tiotropium bromide, that is delivered in a single actuation can be any suitable dose depending on the nature of the condition and patient population that the inhaler is designed to treat. Typically, the total dose delivered, in micrograms, is no less than 0.5, no less than 1, no less than 1.5, or no less than 3, such as no less than 3.25, no less than 3.75, no less than 4, or no less than 4.25. Typically, the total dose delivered, in micrograms, is no more than 7.5, no more than 7.25, no more than 7.0, no more than 6.5, no more than 6.25, no more than 6.0, no more than 5.75, no more than 5.5, no more than 5.25, no more than 5, no more than 4.75, no more than 4.0, no more than 3.5, no more than 3.0, or no more than 2.0. Most commonly, the dose is from 4 micrograms to 5.5 micrograms per actuation.

Typical inhalers, such as metered dose inhalers, are designed to deliver a specified number of doses of the pharmaceutical formulation. A dose is sometimes deliverable by a single actuation of the inhaler, but can also be deliverable by two, three, four, or more actuations. In most cases, the specified number of doses is from 10 to 100, such as from 20-40. One commonly employed metered dose inhaler is designed to provide 30 doses whereby each dose is delivered in two actuations; this can be employed with any of the formulations or inhaler types described herein.

The inhaler, particularly when it is a metered dose inhaler, can contain a dose counter for counting the number of doses. Suitable dose counters are known in the art, and are described in, for example, US8740014, US8479732, US20120234317, and US8814035, all of which are incorporated by reference for their disclosures of dose counters.

One exemplary dose counter, which is described in detail in US 8740014 (which is hereby incorporated by reference for its disclosure of the dose counter) has a fixed ratchet element and a trigger element that is constructed and arranged to undergo reciprocal movement coordinated with the reciprocal movement between an actuation element in an inhaler and the dose counter. The reciprocal movement typically comprises an outward stroke (outward being with respect to the inhaler) and a return stroke. The return stroke returns the trigger element to the position that it was in prior to the outward stroke. A counter element is also included in this type of dose counter. The counter element is constructed and arranged to undergo a predetermined counting movement each time a dose is dispensed. The counter element is biased towards the fixed ratchet and trigger elements and is capable of counting motion in a direction that is substantially orthogonal to the direction of the reciprocal movement of the trigger element.

The counter element in the above-described dose counter comprises a first region for interacting with the trigger member. The first region comprises at least one inclined surface that is engaged by the trigger member during the outward stroke of the trigger member. This engagement during the outward stroke causes the counter element to undergo a counting motion. The counter element also comprises a second region for interacting with the ratchet member. The second region comprises at
least one inclined surface that is engaged by the ratchet element during the return stroke of the trigger
element causing the counter element to undergo a further counting motion, thereby completing a
counting movement. The counter element is normally in the form of a counter ring, and is advanced
partially on the outward stroke of the trigger element, and partially on the return stroke of the trigger
element. As the outward stroke of the trigger typically corresponds to the depression of a valve stem
that causes firing of the valve (and, in the case of a metered dose inhaler, also meters the contents) and
the return stroke typically corresponds to the return of the valve stem to its resting position, this dose
counter allows for precise counting of doses.

Another suitable dose counter, which is described in detail in US8479732 (which is incorporated
by reference for its disclosure of dose counters) is specially adapted for use with a metered dose
inhaler. This dose counter includes a first count indicator having a first indicia bearing surface. The
first count indicator is rotatable about a first axis. The dose counter also includes a second count
indicator having a second indicia bearing surface. The second count indicator is rotatable about a
second axis. The first and second axes are disposed such that they form an obtuse angle. The obtuse
angle mentioned above can be any obtuse angle, but is advantageously 125 to 145 degrees. The
obtuse angle permits the first and second indicia bearing surface to align at a common viewing area to
collectively present at least a portion of a medication dosage count. One or both of the first and
second indicia bearing surfaces can be marked with digits, such that when viewed together through
the viewing area the numbers provide a dose count. For example, one of the first and second indicia
bearing surface may have "hundreds" and "tens" place digits, and the other with "ones" place digits,
such that when read together the two indicia bearing surfaces provide a number between 000 and 999
that represents the dose count.

Yet another suitable dose counter is described in US 20120234317 (hereby incorporated by
reference for its disclosure of dose counters). Such a dose counter includes a counter element that
undergoes a predetermined counting motion each time a dose is dispensed. The counting motion is
typically vertical or essentially vertical. A count indicating element is also included. The count
indicating element, which undergoes a predetermined count indicating motion each time a dose is
dispensed, includes a first region that interacts with the counter element.

The counter element has regions for interacting with the count indicating element. Specifically,
the counter element comprises a first region that interacts with a count indicating element. The first
region includes at least one surface that it engaged with at least one surface of the first region of the
aforementioned count indicating element. The first region of the counter element and the first surface
of the count inducing element are disposed such that the count indicating member completes a count
indicating motion in coordination with the counting motion of the counter element, during and
induced by the movement of the counter element, the count inducing element undergoes a rotational
or essentially rotational movement. In practice, the first region of the counter element or the counter
indicating element can comprise, for example, one or more channels. A first region of the other element can comprise one or more protrusions adapted to engage with said one or more channels.

Yet another dose counter is described in US 8814035 (hereby incorporated by reference for its disclosure of dose counters). Such a dose counter is specially adapted for use with an inhaler with a reciprocal actuator operating along a first axis. The dose counter includes an indicator element that is rotatable about a second axis. The indicator element is adapted to undergo one or more predetermined count-indicating motions when one or more doses are dispensed. The second axis is at an obtuse angle with respect to the first axis. The dose counter also contains a worm rotatable about a worm axis. The worm is adapted to drive the indicator element. It may do this, for example, by containing a region that interacts with and enmeshes with a region of the indicator element. The worm axis and the second axis do not intersect and are not aligned in a perpendicular manner. The worm axis is also, in most cases, not disposed in coaxial alignment with the first axis. However, the first and second axes may intersect.

At least one of the various internal components of an inhaler, such as a metered dose inhaler, as described herein, such as one or more of the canister, valve, gaskets, seals, O-rings, and the like, can be coated with one or more coatings. Some of these coatings provide a low surface energy. Such coatings are not required because they are not necessary for the successful operation of all inhalers.

Some coatings that can be used are described in US8414956, US8815325 and United States Patent Application Number US20120097159, all of which are incorporated by reference for their disclosure of coatings for inhalers and inhaler components.

A first acceptable coating can be provided by the following method:

a) providing one or more component of the inhaler, such as the metered dose inhaler,

b) providing a primer composition comprising a silane having two or more reactive silane groups separated by an organic linker group,

c) providing a coating composition comprising an at least partially fluorinated compound,

d) applying the primer composition to at least a portion of the surface of the component,

e) applying the coating composition to the portion of the surface of the component after application of the primer composition.

The at least partially fluorinated compound will usually comprise one or more reactive functional groups, with the or each one reactive functional group usually being a reactive silane group, for example a hydrolysable silane group or a hydroxy silane group. Such reactive silane groups allow reaction of the partially fluorinated compound with one or more of the reactive silane groups of the primer. Often such reaction will be a condensation reaction.

One exemplary silane that can be used has the formula

$$X_{3-m} (R^1)_m Si - Q - Si(R^2)_k X_{3-k}$$
wherein R^1 and R^2 are independently selected univalent groups, X is a hydrolysable or hydroxy group, m and k are independently 0, 1, or 2 and Q is a divalent organic linking group.

Useful examples of such silanes include one or a mixture of two or more of 1,2-bis(trialkoxysilyl) ethane, 1,6-bis(trialkoxysilyl) hexane, 1,8-bis(trialkoxysilyl) octane, 1,4-bis(trialkoxysilyl)benzene,bis(trialkoxysilyl)itaconate, and 4,4'-bis(trialkoxysilyl)-1,1'-diphenyl, wherein any trialkoxy group may be independently trimethoxy or triethoxy.

The coating solvent usually comprises an alcohol or a hydrofluoroether.

If the coating solvent is an alcohol, preferred alcohols are C_1 to C_4 alcohols, in particular, an alcohol selected from ethanol, n-propanol, or iso-propanol or a mixture of two or more of these alcohols.

If the coating solvent is a hydrofluoroether, it is preferred that the coating solvent comprises a C_4 to C_8 hydrofluoroether. Generally, the hydrofluoroether will be of formula

$$C g F_2 g + i O Ch H_2 h \_i$$

wherein g is 2, 3, 4, 5, or 6 and h is 1, 2, 3 or 4. Examples of suitable hydrofluoroethers include those selected from the group consisting of methyl perfluoropropyl ether, ethyl perfluoroisopropyl ether, methyl nonafluorobutylether, ethyl nonafluorobutylether and mixtures thereof.

The polyfluoropolyether silane is typically of the formula

$$R^\prime Q_{n_i} [Q^2 o_{w=1} [C(R^4)_{w=2} Si(X)_{w=2} (R^5)_{w=2} ]_{z} ]$$

wherein:

- R' is a polyfluoropolyether moiety;
- Q^1 is a trivalent linking group;
- each Q^2 is an independently selected organic divalent or trivalent linking group;
- each R^4 is independently hydrogen or a C_4 alkyl group;
- each X is independently a hydrolysable or hydroxyl group;
- R^5 is a C_4 alkyl or phenyl group;
- v and w are independently 0 or 1, x is 0 or 1 or 2; y is 1 or 2; and z is 2, 3, or 4.

The polyfluoropolyether moiety R'can comprise perfluorinated repeating units selected from the group consisting of -(C F_{10}^{n-2n})-, (CF(Z)0)-, -(CF(Z)C F_{12}^{n-2n})-,(C F_{12}^{n-2n} CF(Z)O)-,(C F_{14}^{n-2n} CF(Z)O) and combinations thereof; wherein n is an integer from 1 to 6 and Z is a perfluoroalkyl group, an oxygen-containing perfluoroalkyl group, a perfluoroalkoxy group, or an oxygen-substituted perfluoroalkoxy group, each of which can be linear, branched, or cyclic, and have 1 to 5 carbon atoms and up to 4 oxygen atoms when oxygen-containing or oxygen-substituted and wherein for repeating units including Z the number of carbon atoms in sequence is at most 6. In particular, n can be an integer from 1 to 4, more particularly from 1 to 3. For repeating units including Z the number of carbon atoms in sequence may be at most four, more particularly at most 3. Usually, n is 1 or 2 and Z is an -CF_3.
group, more wherein \( z \) is 2, and \( R' \) is selected from the group consisting of -
\[
-CF_2O(CF_2O)_m(C_F_4O)^pCF_2\cdot ,
\]
\[
-CF(CF_3)_0(CF(CF_3)_CF_2)_{p}CF(CF_3)_{-},
\]
\[
-CF_2O(CF(CF_3)_CF_2)_{p}CF(CF_3)_{-},
\]
\[
-OCF_2FCF(CF_3)_pO-CF_2_{t,}0(CF(CF_3)CF_2)_{p}CF(CF_3)_{-},
\]
wherein \( t \) is 2, 3 or 4 and wherein \( m \) is 1 to 50, and \( p \) is 3 to 40.

A cross-linking agent can be included. Typical cross-linking agents include tetramethoxysilane; tetraethoxysilane; tetrapropoxysilane; methyl triethoxysilane; dimethyldiethoxysilane; octadecyliethoxysilane; 3-glycidoxy-propyltrimethoxysilane; 3-glycidoxy-propyltriethoxy silane; 3-aminopropyl 1-trimethoxysilane; 3-aminopropyl 1-triethoxysilane; bis (3-trimethoxysilylpropyl) amine; 3-aminopropyl tri(methoxyethoxyethoxy) silane; \( N \) (2-aminoethyl) 3-aminopropyltrimethoxysilane; bis (3-trimethoxysilylpropyl) ethylenediamine; 3-mercaptopropyltrimethoxysilane; 3-mercaptopropyltriethoxy silane; 3-trimethoxysilyl-propylmethacrylate; 3-triethoxysilylpropylmethacrylate; bis (trimethoxysilyl) itaconate; allyltriethoxysilane; allyltrimethoxy silane; 3-(N-allylamino)propyltrimethoxysilane; vinyltrimethoxy silane; vinyltriethoxysilane; and mixtures thereof.

The component to be coated can be pre-treated before coating, typically by cleaning. Cleaning can be by way of a solvent, typically a hydrofluorooether, e.g. HFE72DE, or an azeotropic mixture of about 70% w/w trans-dichloroethylene; 30% w/w of a mixture of methyl and ethyl nonafluorobutyl and nonafluoroisobutyl ethers.

The above-described first acceptable coating is particularly useful for coating valves components, including one or more of valve stems, bottle emptiers, springs, and tanks, as well as canisters, such as metered dose inhalers, as described herein. This coating system can be used with any type of inhaler and any formulation described herein.

A second type of coating that can be used comprises a polyphenylsulphone. The polyphenylsulphone typically has the following chemical structure

![Chemical Structure](image)

In this structure, \( n \) is the number of repeat units, which is typically sufficient to provide a weight average molecular weight from 10,000 to 80,000 daltons, for example, from 10,000 to 30,000 daltons.

Other polymers, such as polyethersulphones, fluoropolymers such as PTFE, FEP, or PFA, can also be included. However, such other polymers are optional, and it is often advantageous to exclude them.
Polyphenylsulphones can be difficult to apply by a solvent casting process. Thus, a special solvent system that is viable for use in a manufacturing setting can be employed for coating the polyphenylsulphones. On such solvent system employs a (1) first solvent that has a Hildebrand Solubility Parameter of at least 20.5 MPa$^{0.5}$ and at most 25 MPa$^{0.5}$; and (2) at least 20% by volume, often greater than 70% or greater than 80% by volume, of at least one 5-membered aliphatic, cyclic, or heterocyclic ketone based on the total volume of the solvent system. Optionally, a third component, namely a linear aliphatic ketone, can be included in amounts less than 5% by volume of the total volume of the solvent system.

Any first solvent that has a Hildebrand Solubility Parameter of at least 20.5 MPa$^{0.5}$ and at most 25 MPa$^{0.5}$ can be used, so long as the other components of the solvent system are as stated above. Some such first solvents are also 5-membered aliphatic, cyclic, or heterocyclic ketones, in which case the first solvent and the 5-membered aliphatic, cyclic, or heterocyclic ketone can be the same material. Other such solvents include acetonitrile.

The 5-membered aliphatic, cyclic, or heterocyclic ketone is typically a gamma lactone, such as gamma-butyrolactone, or a gamma lactam, such as a pyrrolidone like 2-pyrrolidone, or an alkyl substituted 2-pyrrolidone like N-alkyl-2-pyrrolidones such as N-methyl-2-pyrrolidine (sometimes known by the acronym NMP). Other examples of 5-membered aliphatic, cyclic, or heterocyclic ketone that can be used include 2-methyl cyclopentanone, 2-ethyl cyclopentanone, and 2-[1-(5-methyl-2-furyl)butyl]cyclopentanone. Cyclopentanone is the most commonly used material.

The optional linear aliphatic ketone can be any linear aliphatic ketone, and is typically acetone, although methyl ethyl ketone is also frequently employed.

The above-described second acceptable coating can be used on any type of inhaler, but is particularly useful for components of metered dose inhalers.

A third acceptable coating can be used to lower the surface energy of any component of an inhaler, such as a metered dose inhaler, but is particularly useful for valve stems, particularly those made of acetal polymer, as well as for stainless steel or aluminum components, particularly those used in canisters.

Such a coating can be formed on a component of an inhaler by the following process:

a) forming a non-metal coating on at least a portion of a surface of the medicinal inhalation device or a component of a medicinal inhalation device, respectively, said coating having at least one functional group;

b) applying to at least a portion of a surface of the non-metal coating a composition comprising an at least partially fluorinated compound comprising at least one functional group; and

c) allowing at least one functional group of the at least partially fluorinated compound to react with at least one functional group of the non-metal coating to form a covalent bond.
The at least one functional group of the non-metal coating is typically a hydroxyl group or silanol group. In most cases, the non-metal coating has a plurality of functional groups, particularly silanol groups, and can be formed, for example by plasma coating an organosilicone with silanol groups on the inhaler or one or more inhaler components. Typical organosilicon compounds include trimethylsilane, triethylsilane, trimethoxysilane, triethoxysilane, tetramethylsilane, tetraethylsilane, tetrabromoethylsilane, tetraethoxysilane, hexamethyldisiloxane, tetramethylcycloctetrasiloxane, tetraethylyclocotetrasiloxane, octamethylcycloctetrasiloxane, hexamethyldisiloxane, bistrimethylsilylmethane, and mixtures thereof. Most commonly, one or more of trimethylsilane, triethylsilane, tetramethylsilane, tetraethylsilane, bistrimethylsilylmethane are employed, with tetramethylsilane being most common. In addition to the organosilicon, the plasma can contain one or more of oxygen, a silicon hydride, particularly silicon tetrahydride, disilane, or a mixture thereof, or both. After deposition, the non-metal coating can be a diamond like glass or carbon like glass containing, on a hydrogen free basis, at 20 atomic percent or more of carbon and 30 atomic percent of more of silicon and oxygen combined.

The non-metal coating is often exposed to an oxygen plasma or corona treatment before applying the partially fluorinated compound. Most typically, an oxygen plasma treatment under ion bombardment conditions is employed.

The at least partially fluorinated compound often contains one or more hydrolysable groups, such as oxyalkly silanes, typically ethoxy or methoxy silanes. A polyfluoropolyether segment, which in particular cases is a perfluorinated polyfluoroether, is typically used. Poly(perfluoroethylene) glycol is most common. Thus, the at least partially fluorinated compound can include a polyfluoropolyether linked to one or more functional silanes by way of, for example, a carbon-silicon, nitrogen-silicon, or sulfur-silicon.

Examples of at least partially fluorinated compounds that can be used include those having the following formula:

\[ R_1\{Q-[C(R)_{2-n}Si(Y)_{3-n}(R^1a)_{n}]_x \} \]

wherein:
- \( R_1 \) is a monovalent or multivalent polyfluoropolyether segment;
- \( Q \) is an organic divalent or trivalent linking group;
- each \( R \) is independently hydrogen or a \( C_{1-6} \) alkyl group;
- each \( Y \) is independently a hydrolysable group;
- \( R^1a \) is a \( C_{8} \) alkyl or phenyl group;
- \( x \) is 0 or 1 or 2;
- \( y \) is 1 or 2; and
- \( z \) is 1, 2, 3, or 4.

Typically, \( R_1 \) comprises perfluorinated repeating units selected from the group consisting of -\((C_{1,2,3,0})\).
-{CF(Z)O}-, -(CF(Z)CnF2nO)-, -(CnF2nCF(Z)0)-, -(CF2CF(Z)0)-, and combinations thereof; wherein n
is an integer from 1 to 6 and Z is a perfluoroalkyl group, an oxygen-containing perfluoroalkyl group, a
perfluoroalkoxy group, or an oxygen-substituted perfluoroalkoxy group, each of which can be linear, branched, or cyclic, and have 1 to 5 carbon atoms and up to 4 oxygen atoms when oxygen-containing
or oxygen-substituted and wherein for repeating units including Z the number of carbon atoms in
sequence is at most 6. Particular examples of this compound are those where z is 1. Rf is selected
from the group consisting of C3FvO(CF3)CF20)pCF(CF3)-, CF30(C2F40)pCF2-, C3F70(C2F2pCF20)pCF
-C2F2-, C3F700(CF2CF20)pCF(CF3)- and CF30(C2FCF30)pCF-C20X-, wherein X is CF2-, C2F4-.

C3F6-, C4F8- and wherein the average value of p is 3 to 50. Other particular examples include
those wherein z is 2, Rf is selected from the group consisting of -CF20(CF20)m(C2F40)pCF2-, -
CF(CF3)0(CF(CF3)CF20)pCF(CF3)-, -CF20(C2Fk0)pCF2-, -CF20(C2Fk0)pCF(CF3)-, (OCF2CF(CF3))pO-C
F2t-0(CFCF(CF20)pCF(CF3)- wherein t is 2, 3 or 4 and wherein m is 1 to 50, and p is 3 to 40. Most commonly Rf is one of -CF20(CF20)m(C2F40)pCF2-, -CF20(C2F40)pCF2-, and
-CF(CF3)0(COCF2CF(CF3))pO-(OCF2CF(CF3))pCF(CF3)- wherein t is 2, 3, or 4, and the average value
of m+p or p+p or p is from about 4 to about 24. Q is commonly selected from the group consisting of
-C(0)N(R)-(CH2)k-, -S(0)2N(R)-(CH2)k-, -(CH2)k-, -CH20-(CH2)k-, -C(0)S-(CH2)k-, -CH2OC(0)(R)-(CH2)k-, and
-CH2OCH2CHCH2OC(0)NH(CH2)3——

OC(0)NH(CH2)3——

when R is hydrogen or C1-4 alkyl, and k is 2 to about 25. In other common cases, Q is selected from
the group consisting of
-C(0)N(R)(CH2)2-, -OC(0)(R)(CH2)2-, -CH20(CH2)2-, or -CH2OC(0)(R)-(CH2)2-, R is hydrogen
or C1-4 alkyl, and y is 1.

Upon applying appropriate at least partially fluorinated compounds to the non-metallic coating,
at least one covalent bond can form between the two, thereby completing the coating.

Yet another suitable coating is fluorinated ethylene propylene copolymer, sometimes known as
FEP. FEP coatings are particularly useful for coating one or more internal surfaces of a canister.

List of Exemplary Embodiments

The following embodiments are meant to be illustrative, and are not intended to be limiting
unless otherwise specified.

1. A composition comprising

tiotropium or a pharmaceutically acceptable salt or solvate thereof in a concentration of 0.05
mg/ml to 0.15 mg/ml based on the mass of tiotropium bromide;

citric acid or a salt thereof in a concentration of 0.10 wt% to 0.2 wt% based on the weight of citric
acid;
glycerol in a concentration of 0.5 wt% to 2.0 wt%;
ethanol in a concentration up to 20 wt%; and
a propellant consisting essentially of 1,1,1,2-tetrafluoroethane; wherein
the composition is in the form of a solution.

2. A composition comprising
tiotropium or a pharmaceutically acceptable salt or solvate thereof in a concentration of 0.0075 wt.% to 0.015 wt.% based on the weight of tiotropium bromide;
citric acid or a salt thereof in a concentration of 0.12 wt% to 0.2 wt% based on the weight of free citric acid;
glycerol in a concentration of 0.5 wt% to 2.0 wt%;
ethanol in a concentration of 10 wt% to 20 wt%; and
a propellant consisting essentially of 1,1,1,2-tetrafluoroethane; wherein
the composition is in the form of a solution.

3. The composition of any of the preceding embodiments, wherein the tiotropium or a pharmaceutically acceptable salt or solvate thereof is a pharmaceutically acceptable salt of tiotropium.

4. The composition of any of the preceding embodiments, wherein the tiotropium or a pharmaceutically acceptable salt or solvate thereof is a tiotropium bromide.

5. The composition of any preceding embodiment, wherein the tiotropium bromide is anhydrous tiotropium bromide.

6. The composition of any of the preceding embodiments, wherein tiotropium is in solution.

7. The composition of any of the preceding embodiments, wherein the concentration of tiotropium, expressed in terms of tiotropium bromide, is no more than 0.15 mg/ml, no more than 0.14 mg/ml, no more than 0.13 mg/ml, no more than 0.12 mg/ml, no more than 0.11 mg/ml, no more than 0.10 mg/ml, no more than 0.09 mg/ml, no more than 0.08 mg/ml, no more than 0.07 mg/ml, no more than 0.06 mg/ml, or no more than 0.05 mg/ml.

8. The composition of any of the preceding embodiments, wherein the concentration of tiotropium, expressed in terms of tiotropium bromide, can be no less than 0.05 mg/ml, no less than 0.06 mg/ml, no less than 0.07 mg/ml, no less than 0.08 mg/ml, no less than 0.09, no less than 0.1 mg/ml, no less than 1.1 mg/ml, no less than 1.2 mg/ml, or no less than 1.3 mg/ml.

9. The composition of any of the preceding embodiments, wherein the concentration tiotropium, expressed in terms of tiotropium bromide, is about 0.08 mg/ml to about 0.012 mg/ml, 0.08 mg/ml to 0.12 mg/ml, about 0.09 mg/ml to about 0.11 mg/ml, or 0.09 mg/ml to 0.11 mg/ml.

9a. The composition of any of the preceding embodiments, wherein the concentration of tiotropium, expressed in terms of tiotropium bromide, is about 0.1 mg/ml or 0.1 mg/ml.

9b. The composition of any preceding embodiment, wherein the concentration of tiotropium expressed as wt% is no less than 0.0075, no less than 0.008, no less than 0.009, or no less than 0.01.
9c. The composition of any of the preceding embodiments wherein the concentration of tiotropium expressed as wt% is no greater than 0.015, no greater than 0.014, no greater than 0.0125, or no greater than 0.012.

10. The composition of any of the preceding embodiments wherein the weight percent of ethanol is no greater than 20, no greater than 19, no greater than 18, no greater than 17, no greater than 16, no greater than 15.5, no greater than 15, no greater than 14.5, no greater than 14, no greater than 13, no greater than 12, no greater than 11, or no greater than 10.

11. The composition of any of the preceding embodiments, wherein the weight percent of ethanol is no less than 10, no less than 11, no less than 12, no less than 13, no less than 14, no less than 14.5, no less than 15, no less than 15.5, no less than 16, no less than 17, or no less than 18.

12. The composition of any of the preceding embodiments wherein the weight percent of ethanol is from about 13 to about 17, 13 to 17, about 14 to about 16, 14 to 16, about 14.5 to about 15.5, or 14.5 to 15.5.

13. The composition of any of the preceding embodiments, wherein the weight percent of ethanol is about 15 or more particularly 15.

14. The composition of any of the preceding embodiments, wherein the weight percent of citric acid or salt thereof, based on the weight of citric acid, is no less than 0.075%, no less than 0.08%, no less than 0.09%, no less than 0.10%, no less than 0.11%, no less than 0.12%, no less than 0.13%, no less than 0.14%, no less than 0.15%, no less than 0.16%, no less than 0.17%, no less than 0.18%, no less than 0.19%, or no less than 0.20%.

15. The composition of any of the preceding embodiments, wherein the weight percent of citric acid or salt thereof, based on the weight of citric acid, is no more than 0.20%, no more than 0.19%, no more than 0.18%, no more than 0.17%, no more than 0.16%, no more than 0.15%, no more than 0.14%, no more than 0.13%, no more than 0.12%, no more than 0.11%, no more than 0.1%, or no more than 0.09%.

16. The composition of any of the preceding embodiments, wherein the weight percent of citric acid or salt thereof, based on the weight of citric acid, is 0.12% to about 0.18%, 0.12% to 0.18%, about 0.13% to about 0.17%, 0.13% to 0.17%, about 0.14% to about 0.16%, 0.14% to 0.16%, about 0.15%, or 0.15%.

17. The composition of any of the preceding embodiments, wherein the weight percent of citric acid or salt thereof, based on the weight of citric acid, is, about 0.15%, or 0.15%.

18. The composition of any of the preceding embodiments, wherein the citric acid or salt thereof is citric acid.
19. The composition of any of the preceding embodiments, wherein glycerol is present, on a weight percent basis, in an amount no more than 2.0%, no more than 1.9%, no more than 1.8%, no more than 1.7%, no more than 1.6%, no more than 1.55%, no more than 1.5%, no more than 1.45%, no more than 1.4%, no more than 1.3%, no more than 1.2%, no more than 1.1%, no more than 1.0%, no more than 0.9%, no more than 0.8%, or no more than 0.75%. Thus, the ex-actuator size affecting compound, particularly glycerol, can be present, on a weight percent basis, in about 0.7% to about 1.7%, 0.7% to 1.7%, about 0.8% to 1.6%, 0.8% to 1.6%, about 0.9 to about 1.6, 0.9 to 1.6%, about 1.0% to about 1.5%, or 1.0% to 1.5%.

20. The composition of any of the preceding embodiments, wherein glycerol is present, on a weight percent basis, in an amount no less than 1.0%, no less than 1.1%, no less than 1.2%, no less than 1.3%, no less than 1.4%, no less than 1.45%, no less than 1.5%, no less than 1.55%, no less than 1.6%, no less than 1.7%, no less than 1.8%, or no less than 1.9%.

21. The composition of any of the preceding embodiments wherein the glycerol is present, on a weight percent basis, in about 0.7% to about 1.7%, 0.7% to 1.7%, about 0.8% to 1.6%, 0.8% to 1.6%, about 0.9% to about 1.6%, or 0.9% to 1.6%.

22. The composition of any of the preceding embodiments wherein the glycerol is present, on a weight percent basis, is about 1.0% to about 1.5%, or 1.0% to 1.5%.

23. The composition of embodiment 22 wherein the glycerol is present, on a weight percent basis, in about 1.0%, more particularly 1%, or wherein the glycerol is present, on a weight percent basis, in about 1.5%, more particularly 1.5%.

24. The composition of any preceding embodiment wherein the composition loses less than 5 wt% of the tiotropium content after six months of storage inside an aerosol canister at a temperature of 25°C and a relative humidity of 60%.

25. The composition of any of the preceding embodiments, wherein the amount of 1,1,1,2-tetrafluoroethane in the propellant is, on a weight percent basis, at least 95% .

26. The composition of any of the preceding embodiments, wherein the propellant is 1,1,1,2-tetrafluoroethane .

27. An aerosol canister containing a formulation of any preceding embodiment under a pressure that is greater than ambient atmospheric pressure.

28. The aerosol canister of embodiment 27 comprising at least one surface having a primer composition comprising a silane having two or more reactive silane groups separated by an organic linker group disposed thereon, wherein the primer composition has a coating composition comprising an at least partially fluorinated compound disposed thereon.
29. The aerosol canister of embodiment 28, wherein the at least partially fluorinated compound is an at least partially fluorinated polyethersilane.

30. An aerosol canister of embodiment 27 comprising at least one surface having a coating comprising polyphenylsulphone.

31. An aerosol canister of embodiment 27 comprising at least one surface having a coating comprising a diamond like glass or carbon like glass.

32. An inhaler comprising the composition of any of embodiments 1-26 or the aerosol canister of any of embodiments 27-31.

33. The inhaler of embodiment 32 that is a metered dose inhaler.

34. The inhaler of any of embodiments 32-33 comprising a valve stem.

35. The inhaler of any of embodiments 32-34 comprising a dose counter.

36. A method of making a composition of any of embodiments 1-26, comprising admixing anhydrous tiotropium bromide, anhydrous ethanol, anhydrous glycerol, and anhydrous propellant.

37. The method of embodiment 36, further comprising the step of dissolving the anhydrous tiotropium bromide in the composition.


39. The method of embodiment 38, wherein at least a part of the composition of any of embodiments 1-26 is cold-filled into the canister.

40. The method of embodiment 38, wherein at least a part of the composition of any of embodiments 1-26 is filled into the canister under the application of pressure greater than atmospheric pressure.

41. A composition comprising
   tiotropium or a pharmaceutically acceptable salt or solvate thereof in a concentration of 0.0075 wt.% to 0.015 wt.% based on the weight of tiotropium bromide;
   citric acid or a salt thereof in a concentration of 0.12 wt% to 0.2 wt% based on the weight of free citric acid;
   ethanol in a concentration of 10 wt% to 20 wt%; and
   a propellant consisting essentially of 1,1,1,2-tetrafluoroethane; wherein the composition is in the form of a solution.

42. A composition consisting essentially of
   tiotropium or a pharmaceutically acceptable salt or solvate thereof in a concentration of 0.0075 wt.% to 0.015 wt.% based on the weight of tiotropium bromide;
citric acid or a salt thereof in a concentration of 0.12 wt% to 0.2 wt% based on the weight of free citric acid;
ethanol in a concentration of 10 wt% to 20 wt%; and
a propellant consisting essentially of 1,1,1,2-tetrafluoroethane; wherein
the composition is in the form of a solution.

43. A composition consisting of
tiotropium or a pharmaceutically acceptable salt or solvate thereof in a concentration of 0.0075 wt.% to 0.015 wt.% based on the weight of tiotropium bromide;
citric acid or a salt thereof in a concentration of 0.12 wt% to 0.2 wt% based on the weight of free citric acid;
ethanol in a concentration of 10 wt% to 20 wt%; and
a propellant consisting essentially of 1,1,1,2-tetrafluoroethane; wherein
the composition is in the form of a solution.

44. The composition of any of the embodiments 41-43, wherein the tiotropium or a pharmaceutically acceptable salt or solvate thereof is a tiotropium bromide.

45. The composition of any of the embodiments 41-44, wherein the tiotropium bromide is anhydrous tiotropium bromide.

46. The composition of any of the embodiments 41-45, wherein the concentration of tiotropium expressed as wt% is no less than 0.0075, no less than 0.008, no less than 0.009, or no less than 0.01.

47. The composition of any of the embodiments 41-46, wherein the concentration of tiotropium expressed as wt% is no greater than 0.015, no greater than 0.014, no greater than 0.0125, or no greater than 0.012.

48. The composition of any of the embodiments 41-47, wherein the weight percent of citric acid or salt thereof, based on the weight of citric acid, is 0.12% to about 0.18%, 0.12% to 0.18%, about 0.13% to about 0.17%, 0.13% to 0.17%, about 0.14% to about 0.16%, 0.14% to 0.16%, about 0.15%, or 0.15%.

49. The composition of any of the embodiments 1-16 and 41-48, wherein the weight percent of citric acid or salt thereof, based on the weight of citric acid, is 0.125 wt% to 0.175 wt%.

50. The composition of any of the embodiments 41-49, wherein the weight percent of citric acid or salt thereof, based on the weight of citric acid, is, about 0.15%, or 0.15%.

51. The composition of any of the embodiments 41-50 wherein the weight percent of ethanol is from about 13 to about 17, 13 to 17, about 14 to about 16, 14 to 16, about 14.5 to about 15.5, or 14.5 to 15.5.
52. The composition of any of the embodiments 41-51, wherein the weight percent of ethanol is about 15 or more particularly 15.

53. An aerosol canister containing a composition of any of the embodiments 41-52 under a pressure that is greater than ambient atmospheric pressure.

54. The aerosol canister of embodiment 53 comprising at least one surface having a primer composition comprising a silane having two or more reactive silane groups separated by an organic linker group disposed thereon, wherein the primer composition has a coating composition comprising an at least partially fluorinated compound disposed thereon.

55. An inhaler comprising the composition of any of the embodiments 41-52 or the aerosol canister of any of the embodiments 53-54.

56. The inhaler of any of the embodiments 32-35 and 55 comprising an actuator with a nozzle orifice diameter of 0.2 mm to 0.65 mm.

57. The inhaler of any of the embodiments 32-35 and 55 comprising an actuator with a nozzle orifice diameter of 0.2 mm to 0.3 mm.

58. The inhaler of any of the embodiments 32-35 and 55 comprising an actuator with a nozzle orifice diameter of 0.25 mm.

59. The inhaler of any of the embodiments 32-35 and 55 comprising an actuator with a nozzle orifice diameter of 0.3 mm.

EXAMPLES

Examples 1-2 and Prophetic Comparative Examples 1-2

Metered dose inhalers (MDIs) were prepared using 15 mL deep drawn aluminum canisters (3M Corporation, Clitheroe, UK), 50 microliter Bespak PBT valve (BK05 14719, Bespak Europe Ltd, Bergen Way, King's Lynn, Norfolk, PE30 2JJ) fitted with EPDM (ethylene-propylene diene terpolymer elastomer) diaphragm seals, and actuators with orifice diameter range 0.28mm to 0.40mm (Jet Length 0.8mm). The internal surface of each canister was coated with FEP (fluorinated ethylene propylene copolymer). The canisters were cold filled with the formulations shown under the columns Ex. 1 and Ex. 2 in Table 1. The bulk formulation for cold filling individual canisters was prepared by first admixing the citric acid and the ethanol, and then adding the glycerol to the citric acid and ethanol admixture. The tiotropium bromide was then added to the glycerol, citric acid, and ethanol mixture. The HFA-134a propellant was added to a separate batching vessel, and the mixture of tiotropium bromide, glycerol, citric acid, and ethanol was then added to the HFA-134a. The formulation was mixed at -50°C. PCE 1 and PCE2 are prophetic comparative examples.
Table 1.

<table>
<thead>
<tr>
<th>Component</th>
<th>Ex. 1</th>
<th>Ex. 2</th>
<th>PCE 1</th>
<th>PCE 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tiotropium bromide</td>
<td>0.011</td>
<td>0.011</td>
<td>0.011</td>
<td>0.011</td>
</tr>
<tr>
<td>Citric acid</td>
<td>0.150</td>
<td>0.150</td>
<td>0.020</td>
<td>0.020</td>
</tr>
<tr>
<td>Ethanol</td>
<td>15.000</td>
<td>15.000</td>
<td>15.000</td>
<td>15.000</td>
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<tr>
<td>HFA-134a</td>
<td>83.839</td>
<td>83.339</td>
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<tr>
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</tr>
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<td>Total</td>
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<td>100.00</td>
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The aerodynamic particle size distribution emitted from each MDI was evaluated using a Next Generation Impactor Instrument (Copley Scientific Limited, Nottingham, United Kingdom). For each test, an MDI was attached to the throat component (USP Inlet) of the NGI instrument and actuated 10 times into the instrument. Immediately prior to attachment, the MDI was primed by actuating 3 times. The flow rate through the instrument during testing was regulated at 30 L/minute. The test sample (tiotropium) deposited on the valve stem, actuator, throat assembly (USP inlet), individual collection cups 1-7, micro-orifice collector (MOC), and final filter component was collected by rinsing each individual component with a known volume of collection solvent (65/35 (v/v) FhO/methanol. The recovered samples were then analyzed for sample content using a High Performance Liquid Chromatography (HPLC) assay with a reference standard. An Agilent HPLC instrument with an ultraviolet (UV) detector (238 nm) and an X Bridge phenyl 100 x 4.6 mm column (50°C column temp) was used (Waters). An isocratic method was used with the mobile phase being made up of 65% buffer solution (25mmol KH2PO4, adjusted to pH 6.2 with KOH) and 35% methanol. A total of five MDIs were tested for each formulation and the mean ex-actuator size or Mass Median Aerodynamic Diameter (MMAD) for tiotropium was determined using the procedure described in United States Pharmacopia <601>.

The MMAD for the MDI prepared with the formulation of Example 1 was 2.76 microns and the MMAD for the MDI prepared with the formulation of Example 2 was 3.07 microns.

Examples 1 and 2 were solutions when they were produced. After 18 weeks of storage, Examples 1 and 2 remained as solutions, with no observable drug precipitate. The prophetic comparative examples are expected to contain drug precipitate upon observation after 18 weeks of storage; moreover the prophetic comparative examples are not expected to form solutions when initially produced.

Example 3

Metered dose inhalers (MDIs) were prepared using 15 mL deep drawn aluminum canisters (3M Corporation, Clitheroe, UK), 50 microliter Bespak PBT valve (BK05 14719, Bespak Europe Ltd, Bergen Way, King's Lynn, Norfolk, PE30 2JJ) fitted with EPDM (ethylene-propylene diene
terpolymer elastomer) diaphragm seals, and actuators having a nozzle orifice diameter of either 0.25 mm, 0.35 mm, or 0.40 mm (Jet Lengths of 0.8mm). The internal surface of each canister was coated with FEP (fluorinated ethylene propylene copolymer). The canisters were cold filled with the formulation shown under the column Ex. 2 in Table 1. The bulk formulation for cold filling individual canisters was prepared by first admixing the citric acid and the ethanol, and then adding the glycerol to the citric acid and ethanol admixture. The tiotropium bromide was then added to the glycerol, citric acid, and ethanol mixture. The HFA-134a propellant was added to a separate batching vessel, and the mixture of tiotropium bromide, glycerol, citric acid, and ethanol was then added to the HFA-134a. The formulation was mixed at -50 °C.

Example 4

Metered dose inhalers (MDIs) were prepared using 15 mL deep drawn aluminum canisters (3M Corporation, Clitheroe, UK), 50 microliter Bespak PBT valve (BK05 14719, Bespak Europe Ltd, Bergen Way, King's Lynn, Norfolk, PE30 2JJ) fitted with EPDM (ethylene-propylene diene terpolymer elastomer) diaphragm seals, and actuators having a nozzle orifice diameter of either 0.25 mm, 0.40 mm, or 0.45 mm (Jet Lengths of 0.8mm). The internal surface of each canister was coated with FEP (fluorinated ethylene propylene copolymer). The canisters were cold filled with the formulation shown under the column Ex. 3 in Table 2. The bulk formulation for cold filling individual canisters was prepared by first admixing the citric acid and the ethanol. The tiotropium bromide was then added to the citric acid and ethanol mixture. The HFA-134a propellant was added to a separate batching vessel, and the mixture of tiotropium bromide, citric acid, and ethanol was then added to the HFA-134a. The formulation was mixed at -50 °C.

Table 2.

<table>
<thead>
<tr>
<th>Component</th>
<th>Ex. 3 (wt. %)</th>
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<tr>
<td>Tiotropium bromide</td>
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<tr>
<td>Citric acid</td>
<td>0.150</td>
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<td>Ethanol</td>
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<td>HFA-134a</td>
<td>84.839</td>
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<tr>
<td>Total</td>
<td>100.000</td>
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</table>

Example 5

The aerodynamic particle size distribution emitted from each MDI of Examples 3 and 4 was evaluated using a Next Generation Impactor Instrument (Copley Scientific Limited, Nottingham, United Kingdom). For each test, an MDI was attached to the anatomical throat assembly inlet of the NGI instrument and actuated four times into the instrument. Immediately prior to attachment, the MDI was primed by actuating three times. The flow rate through the instrument during testing was
regulated at 30 L/minute. The test sample (tiotropium) deposited on the valve stem, actuator,
anatomical throat assembly, individual collection cups 1-7, micro-orifice collector (MOC), and final
filter component was collected by rinsing each individual component with a known volume of
collection solvent (65/35 (v/v) H2O/methanol. The recovered samples were then analyzed for sample
content using a High Performance Liquid Chromatography (HPLC) assay with a reference standard.
An Agilent HPLC instrument with an ultraviolet (UV) detector (238 nm) and an X Bridge phenyl 100
x 4.6 mm column (50 °C column temp) was used (Waters). An isocratic method was used with the
mobile phase being made up of 65% buffer solution (25mmol KH2PO4, adjusted to pH 6.2 with KOH)
and 35% methanol. A total of three MDIs were tested for each MDI configuration.

The commercial inhalation spray product SPIRIVA RESPIMAT (2.5 meg, tiotropium bromide
inhalation spray) was evaluated as a Comparative Example (Table 3). The device was attached to the
instrument through a coupler and actuated four times. The same procedure as reported above was
followed with the exception that instead of conducting the tests at ambient temperature, the instrument
was cooled to approximately 5 °C during the tests. A total of three devices were tested.

The commercial dry powder inhaler product SPIRIVA HANDIHALER (18 meg, tiotropium
bromide inhalation powder) was also evaluated as a Comparative Example (Table 3). The device was
attached to the instrument through a coupler. Each test was performed using two capsules
(individually administered) with two air intakes for each capsule. The same procedure as reported
above for the MDI examples was followed with the exception that the flow rate was regulated at 39
L/minute, instead of 30 L/minute. A total of three devices were tested.

The following parameters: Fine Particle Mass of collected particles less than 5 micron diameter
("FPM <5"); Fine Particle Mass of collected particles less than 3 micron diameter ("FPM <3"); and
the Impactor Size Mass (ISM) (sum of the sample content from cups 2-7, MOC, and the filter) were
determined (in micrograms) and are reported on a per dose basis (i.e. 2 actuations from an MDI = 1
dose; 2 actuations from a SPIRIVA RESPIMAT device = 1 dose, 1 capsule administered from a
SPIRIVA HANDIHALER device = 1 dose). The mean values (n=3) are reported in Table 3.
"FPM<5" and "FPM<3" were calculated using the CITDAS software program.

<table>
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<tr>
<th>Formulation</th>
<th>NGI Stage Data for MDIs of Examples 3 and 4</th>
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<tr>
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<td>Orifice Diameter of MDI</td>
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<tr>
<td>Ex. 2</td>
<td>0.25 mm</td>
</tr>
<tr>
<td>Ex. 2</td>
<td>0.35 mm</td>
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<tr>
<td>Ex. 2</td>
<td>0.40 mm</td>
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<td>Ex. 3</td>
<td>0.25 mm</td>
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Dissolution testing for each MDI configuration of Example 3 and Example 4 was conducted by collecting the post-throat fraction on a membrane filter (four actuations per MDI). Each filter was evaluated for dissolution using a USP V type apparatus ("Paddle over Disk") and a phosphate buffered saline (PBS) solution bath (200 inL) maintained at 37 °C. The HPLC method described in Example 1 was used to determine the cumulative amount of tiotropium (micrograms) dissolved over time (0-60 minutes). The results are reported in Table 4 as the mean value (n=3) for each MDI configuration.

Table 4.

<table>
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<th>Formulation</th>
<th>Orifice Diameter of MDI</th>
<th>Cumulative Amount Dissolved (micrograms)</th>
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<tr>
<td>Ex. 2</td>
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<td>0.6</td>
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<td>Ex. 2</td>
<td>0.35 mm</td>
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<tr>
<td>Ex. 2</td>
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<td>Ex. 3</td>
<td>0.25 mm</td>
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<td>Ex. 3</td>
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<td>0.6</td>
</tr>
<tr>
<td>Ex. 3</td>
<td>0.45 mm</td>
<td>0.7</td>
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</table>
What is claimed is:

1. A composition comprising
   tiotropium or a pharmaceutically acceptable salt or solvate thereof in a concentration of 0.0075 wt% to 0.15 wt% based on the weight of tiotropium bromide;
   citric acid or a salt thereof in a concentration greater than 0.10 wt% and no greater than 0.2 wt% based on the weight of free citric acid;
   glycerol in a concentration of 0.5 wt% to 2.0 wt%;
   ethanol in a concentration of up to 20 wt%; and
   a propellant consisting essentially of 1,1,2-tetrafluoroethane; wherein the formulation is a solution.

2. The composition of claim 1, wherein the tiotropium or a pharmaceutically acceptable salt or solvate thereof is tiotropium bromide.

3. The composition of any of the preceding claims, wherein the tiotropium is in a concentration of 0.09 wt% to 0.13 wt% based on the weight of tiotropium bromide.

4. The composition of any of the preceding claims, wherein the glycerol is in a concentration of 1.0 wt% to 1.5 wt%.

5. The composition of any of the preceding claims, wherein the ethanol is in a concentration of between 10 wt% and 20 wt%.

6. The composition of any of the preceding claims, wherein the ethanol is in a concentration of about 15%.

7. The composition of any of the preceding claims, wherein the citric acid or salt thereof is citric acid.

8. The composition of any of the preceding claims, wherein the citric acid or salt thereof is in a concentration of 0.125 wt% to 0.175 wt%.

9. The composition of any of the preceding claims, wherein the propellant comprises no less than 95% 1,1,2-tetrafluoroethane.

10. An aerosol canister containing the composition of any of the preceding claims.

11. The aerosol canister of claim 10 comprising an interior surface, the interior surface having a coating thereon.

12. An inhaler comprising the canister of any of claims 10-11.

13. The inhaler of claim 12, further comprising a valve stem.

14. The inhaler of any of claims 12-13, further comprising a dose counter.

15. The inhaler of any of claims 12-14, wherein the inhaler is a metered dose inhaler.
**INTERNATIONAL SEARCH REPORT**

**International application No**
PCT/US2016/058811

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**A. CLASSIFICATION OF SUBJECT MATTER**
INV. A61K47/10 A61K47/12 A61K9/QG A61K31/60

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**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

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**C. DOCUMENTS CONSIDERED TO BE RELEVANT**

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**Date of the actual completion of the international search**
4 January 2017

**Date of mailing of the international search report**
12/01/2017

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**Name and mailing address of the ISA/European Patent Office, P.O. 5618 Patentlaan 2 NL-2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax (+31-70) 340-3016**

**Authorized officer**
Frelichowska, J

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