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This invention relates to single dose dry powder inhalers in which medicament is stored in a capsule and is released by piercing the capsule wall with polymer-coated steel pins. Methods of preparation of polymer-coated piercing means and their use in releasing the medicament from the capsule are described.

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(57) Abstract

This invention relates to single dose dry powder inhalers in which medicament is stored in a capsule and is released by piercing the capsule wall with polymer–coated steel pins. Methods of preparation of polymer–coated piercing means and their use in releasing the medicament from the capsule are described.

Powder Inhaler

This invention relates to single dose dry powder inhalers in which medicament is stored in a capsule prior to release.

It is well-known to pierce capsules with a metal pin or other cutting means in an inhaler. Capsule-cutting means are disclosed for example in DE 39 27 170 and in EP 528 764.

An inhaler for powdered medicaments is described in US patent 3,991,761 (hereafter referred to as Inhaler A). Inhaler A comprises a recess for receiving a capsule, and push buttons are provided which carry sharpened metal pins and are held in position by biasing springs. In use the capsule is pierced by the spring-loaded pins and on release of the push buttons, the pins retract from the perforated capsule allowing medicament to pass out therefrom.

A problem encountered with known capsule-piercing mechanisms is that the cutting means, e.g. metal pin, can become adhered to a capsule wall. This prevents complete release of medicament for inhalation and causes frustration amongst users.

The present applicants have sought to overcome this problem, and have found that a polymer coating applied to the metal pins permits complete release after capsule-puncture.

In one aspect, therefore, this invention provides an inhaler comprising metal capsule-piercing means which is coated with a polymer.

In another aspect this invention provides the use of polymer-coated metal capsule-piercing means in an inhaler for faster, more complete and effective release of a medicament.

According to one aspect of the present invention, there is provided an inhaler comprising polymer-coated steel capsule-piercing means wherein the steel capsule-piercing means are coated with a first coating of a nickel phosphorous alloy and a second coating of a nickel phosphorous alloy containing PTFE particles.

According to another aspect of the present invention, there is provided a method of preparing polymer-coated capsule-piercing means for an inhaler comprising coating the piercing means with a first coating of a nickel phosphorous alloy and a second coating of a nickel phosphorous alloy containing PTFE particles.

According to yet another aspect of the present invention, there is provided use of an electroless nickel composite coating process to coat a PTFE/nickel phosphorous alloy composite layer onto capsule-piercing means for an inhaler.

In accordance with the present invention, piercing means are provided that may have at least one coating of an inert polymer characterized by (i) excellent antiadhesive

properties, i.e. highly lubricating, properties, for example a polymer having a low friction coefficient, e.g. a friction coefficient (which is defined as the dimensionless quotient obtained by dividing the value of the force necessary to move one body over another at a constant speed by the weight of the body) of at least 0.1 under light loads and (ii) high thermal and chemical inertness. Preferred polymers include any inert polymer, for example fluorocarbon polymers containing $-CF_2-CF_2-$ units, including copolymers thereof, having different terminal groups at the polymer chain ends, for example hydrogen, a halogen, a halogenated carbon, e.g. trichlorocarbon, a carboxylic acid, an alkylgroup, or an alcohol, depending on the method of producing the polymer. Especially preferred is polytetrafluoroethylene (PTFE) also known as TEFLON®. The molecular weights of the polymers used for coating the piercing means may range from about $2x10^3$ to about $2x10^6$ Daltons. Preferably, these polymers are incorporated homogeneously, e.g. uniformly distributed, for example in an alloy matrix, at a concentration of up to 30 %, e.g. from 5 to 30 %. These alloys may contain chromium and/or one or more elements of Group VIII of the Periodic Table, for example iron, cobalt, nickel, preferably nickel, and/or a noble metal, for example ruthenium, rhodium, palladium. Particularly preferred are nickel phosphorous alloys which preferably contain about 90 to 93 % by weight nickel and about 7 to 10 % by weight phosphorous.

Coterminous piercing of the capsule may be achieved by one or more pins at each end of the capsule. The coating or coatings may cover at least the portion of a pin or pins which come in contact and pierce the capsule, but preferably they cover the whole surface of the pin or pins. More than one alloy may be used to apply more than one coating to the pins, particularly preferred are two coatings. The polymer coating or coatings may typically have a total thickness of between about 1 to about 30 microns, for example a first coating may have a thickness of about 5 to about 15 microns, and a second coating may have a thickness of about 3 to 10 microns.

Thus, in one embodiment of this invention, piercing means may be coated with PTFE or an alloy matrix, e.g. a chromium or a nickel phosphorous alloy, or an alloy matrix containing PTFE particles, e.g. a PTFE-containing nickel phosphorous alloy, also known as CHENIFLON™.

In a particularly preferred embodiment of this invention, steel pins, e.g. stainless steel pins, for use in an inhalation device are coated with a first layer of a nickel phosphorous alloy, e.g. NIPLOY™, to a thickness of between about 5 and about 15 microns and a second layer containing about 20 to 30 % by volume PTFE particles homogeneously incorporated in a nickel phosphorous alloy matrix may be applied at a thickness of between 3 and 10 microns onto the first layer.

Preferably, the composition of a plated deposit contains about 80 to 95 %, e.g. 85 % by weight nickel, 5 to 20 %, e.g. 6.6 % by weight phosphorous and up to 30 %, e.g. 8.4 % by weight PTFE. The PTFE content in a composite of 8.4 % by weight may correspond to approximately 25 % by volume in the deposit.

Polymers may be applied to the pins, e.g. steel pins, using techniques suitable to give a uniform coating. Typically, conventional coating techniques include (i) applying the polymers in form of a, preferably fine, dispersion and (ii) evaporating the liquid medium to form the coating. Such techniques include for example

(i) dipping the pins into a dispersion of an alloy and controlling the coating thickness by polymer concentration, rate of dipping and withdrawing, and number of applications;

(ii) wiping or brushing dilute alloy dispersions onto pin surfaces, particularly useful for partial surface coating;

(iii) spraying, for example air spraying of an alloy dispersed in a less volatile solvent using conventional spray equipment, airless spraying using dilute alloy dispersions, or electrostatic spraying;

(iv) depositing a coating using aerosol formulations;

(v) by ultraviolet photopolymerization;

(vi) by RF sputtering; or

(vii) by electrophoresis of such a dispersion onto the pins.

Suitable liquid media to form a dispersion include aqueous solutions, freons, for example dichlorodifluoromethane, dichlorotetrafluoroethane, and the like, including mixtures of these media. The dispersion may be preferably fine such that the particles remain uniformly distributed through the solution with little or no agitation. However,

most preferably the polymer coatings are formed by depositing a coating using plating processes, particularly preferred is an electroless nickel composite coating process.

Typically, in an electroless nickel plating process direct reduction of the nickel onto the surface takes place in solution in the presence of reducing agents which provide the necessary energy, e.g. sodium hypophosphite, boron compounds or hydrazine. Most preferably the reduction reaction is fueled by hypophosphite, which results in co-deposition of small amounts of phosphorous, e.g. up to 10 %, e.g. from about 7 to 10 % by weight. A corresponding composite process further includes particles in the plating solution, for example polymers, e.g. PTFE. Typically a chemical composition of a plating solution may contain 6 g/l nickel metal, 30 g/l sodium hypophosphite, 3-6 g/l PTFE powder, 10-30 g/l organic acids, and stabilizers in picomolar concentrations. Typical operating conditions may include a pH of about 4.7 to 5.0 and a temperature of about 183 to 193 F.

Thus, in a particularly preferred embodiment a coating may be applied by electroless nickel plating or composite coating, e.g. using the Cheniflon™ process from the Argos company of Italy.

The following non-limiting examples were carried out to illustrate the processes of the present invention:

Test 1.

50 Beclometason 400 Cyclocaps® are used successively in Inhaler A with uncoated steel pins at 20°C. After perforation of each capsule the push buttons are released and it is observed that the pins are retained in, or incompletely withdrawn from, 15 capsules.

This is repeated with inhaler A with Niploy™ and Cheniflon™ coated steel pins and no pin retention is observed in any capsule.

Test 2.

50 Salbutanol 200 Cyclocaps® are used successively in Inhaler A with uncoated pins at 20°C. After perforation of each capsule the push buttons are released and the pins are retained in, or incompletely withdrawn from, 18 capsules.

This is repeated with inhaler A with Niploy™ and Cheniflon™ coated pins and no pin retention by any capsule is observed.

CLAIMS:

1. An inhaler comprising polymer-coated steel capsule-piercing means wherein the steel capsule-piercing means are coated with a first coating of a nickel phosphorous alloy and a second coating of a nickel phosphorous alloy containing PTFE particles.

2. An inhaler according to claim 1 wherein the thickness of the first coating is 5 to 15 microns and the thickness of the second coating is 3 to 10 microns.

3. An inhaler as claimed in claim 1 or claim 2 wherein the second coating contains 20 to 30% by volume PTFE particles.

4. A method of preparing polymer-coated capsule-piercing means for an inhaler comprising coating the piercing means with a first coating of a nickel phosphorous alloy and a second coating of a nickel phosphorous alloy containing PTFE particles.

5. Use of an electroless nickel composite coating process to coat a PTFE/nickel phosphorous alloy composite layer onto capsule-piercing means for an inhaler.

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PATENT AGENTS