124

CAVELIER
ABOGADOS

www.cavelier.com
cavelier@cavelier.com

EDIFICIO SISKI
CARRERA 4 No. 72 - 35
BOGOTA 8, COLOMBIA

Teléfono: (57-1) 347 3611
Telefax: (57-1) 211 8650
(57-1) 540 0860
Fax in U.S.A.: (1-305) 381 9660

Señora Jefe de la
DIVISION DE NUEVAS CREACIONES
Superintendencia de Industria y Comercio
E. S. D.

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

Trámite : 011 Evento : 379 Actuación : 444

Referencia	:	Expediente No. 04.044.350
Asunto	:	Solicitud de Patente para **SISTEMA FARMACÉUTICO QUE COMPRENDE UN ADSORBENTE EN UN ENVASE SELLADO**
Solicitante	:	**AVENTIS PHARMA LIMITED**
Fecha de Solicitud	:	13 de mayo de 2004

1. Yo, Emilio FERRERO, obrando como apoderado del solicitante en el asunto antes identificado, me refiero al Oficio No. No. **11673** notificado por fijación en lista del 21 de Septiembre de 2007.

2. Mediante mi memorial de fecha 10 de diciembre de 2007 solicité un plazo de 30 días para atender el Oficio No. **11673.**

3. Mediante el Oficio No. **11673** se puso en conocimiento del solicitante el informe que contiene las observaciones hechas por su Despacho sobre la presente solicitud de patente.

Atiendo a las observaciones de la manera siguiente:

CAVELIER
ABOGADOS

3.1. CLARIDAD DE LA SOLICITUD Y EXCEPCIÓN DE PATENTABILIDAD

Para subsanar las objeciones que sobre claridad y excepciones de patentabilidad hizo su Despacho, presento nuevo pliego reivindicatorio con 35 reivindicaciones en el cual se han hecho los cambios sugeridos por su Despacho, que permiten apreciar claramente el objeto reivindicado en la presente solicitud de patente. Las modificaciones al capitulo reivindicatorio fueron las siguientes:

- El pliego reivindicatorio define con claridad un sistema caracterizado por los elementos que lo componen y la interacción de los mismos, de acuerdo con la información contenida en la descripción. Así, el nuevo pliego incluye todas las características técnicas que permiten a una persona versada en el arte llevar a cabo la invención reivindicada y compararla frente al estado del arte.

- La antigua reivindicación 26 (nueva reivindicación 24) referente al método para prevenir la formación de un aducto se ha redactado de forma tal que se han especificado las etapas del método y las condiciones con las cuales se evita dicha formación del aductos. Así los literales a) y b) de dicha reivindicación han sido incluidos en el preámbulo de la reivindicación

- Con el fin de subsanar la objeción que sobre el título hizo su Despacho, el mismo ha sido modificado a **"SISTEMA FARMACÉUTICO QUE COMPRENDE UN ADSORBENTE EN UN ENVASE SELLADO",** de tal manera que se hace referencia a la propiedad fisicoquímica del sólido señalado en la invención.

- La reivindicación 43 que reclamaba un método de tratamiento ha sido eliminada de éste pliego reivindicatorio.

De esta manera es claro que con las anteriores modificaciones del capítulo reivindicatorio quedan subsanadas las objeciones que por claridad y excepciones de patentabilidad hizo

su Despacho, ya que ahora, dicho pliego reivindica un producto en los términos sugeridos por su Despacho y permite determinar el alcance de la protección reivindicada y compararla frente al estado del arte, de acuerdo con las disposiciones de los artículos 20 (d) y 30 de la Decisión 486.

3.2. UNIDAD DE INVENCIÓN

Su Despacho considera que la solicitud carece de unidad de invención, ya que afirma que se reclaman 3 grupos de invenciones. A saber, (i) las reivindicaciones 1 a 25; (ii) las reivindicaciones 26 a 39; y (iii) las reivindicaciones 40 a 43.

Con el fin de superar esta objeción las reivindicaciones 40 a 43 han sido eliminadas de este pliego reivindicatorio.

Adicionalmente, respetuosamente ponemos de presente que las nuevas reivindicaciones independiente 1 y 24 (antigua reivindicación 26) se relacionan con el concepto de colocar un dispositivo médico (que contiene un medicamento y un componente que libera una sustancia gaseosa que reacciona con el medicamento para formar un aducto) y un material adsorbente dentro de un paquete sellado que es sustancialmente impermeable a las sustancias gaseosas, esto para prevenir la formación de un aducto.

Por lo tanto, con las anteriores modificaciones el nuevo pliego reivindicatorio ahora cumple con el requisito de unidad de invención ya que involucra un único concepto inventivo, por lo tanto queda subsanada la objeción que sobre unidad de invención hizo ese Despacho.

4. ANEXOS:

4.1. Nuevo pliego reivindicatorio con 35 reivindicaciones;
4.2. Formulario de modificaciones;

Industria y Comercio
SUPERINTENDENCIA

Espacio reservado para el adhesivo de radicación

FORMULARIO UNICO DE CORRECCIONES Y MODIFICACIONES

1 SOLICITUD DE:

☐ Corrección de Error Material ☒ Modificación a una solicitud

2 SOLICITANTE

Nombre: AVENTIS PHARMA LIMITED
Sociedad constituida y existente bajo las leyes de Reino Unido.

Dirección: Aventis House,
50 Kings Hill Avenue,
Kings Hill,
West Malling,
Kent ME19 4AH,
Reino Unido

Domicilio: West Malling,
Kent ME19 4AH,
Reino Unido

Teléfono: 546 09 70 **Fax:** 249 40 70
E-mail: clientes@cavelier.com

IDENTIFICACION

C.C. ☐ NIT ☐
C.E. ☐ Otro ☐

Número: _____

3 REPRESENTANTE O APODERADO

Nombre: Emilio FERRERO
Dirección: Carrera 4ª No. 72-35
Teléfono: 347 36 11 **Fax:** 217 92 11
E-mail: cavelier@cavelier.com

IDENTIFICACION

C.C. ☒ NIT ☐
C.E. ☐ Otro ☐

Número: 438.019 TP 31.929

4 Número de expediente: 04.044.350

5 Descripción de la corrección o modificación solicitada:

Presento nuevo capítulo reivindicatorio compuesto por 35 reivindicaciones con el fin de superar las objeciones hechas por Su Despacho a la presente solicitud de patente y pido que el examen de patentabilidad se realice sobre estas nuevas reivindicaciones.

6 Comprobante de pago No. 08-7.427 **Fecha:** 29 de enero de 2008

7 Anexos

☒ Comprobante de pago de la tasa por $103.000.oo por concepto de modificaciones.
☐ Poderes, si fuere el caso
☐ Documento que acredita la existencia y representación legal de las partes, cuando sean personas jurídicas.

8 NOMBRE: EMILIO FERRERO **FIRMA:**

C.C. 438.019 de Usaquén **T.P.A.** 31.929

NNJ

129

Reivindicaciones

1. Un sistema que comprende:

   a) un dispositivo médico que comprende un medicamento y un componente que gradualmente libera una sustancia gaseosa, en donde dicho medicamento es capaz de interactuar con la sustancia gaseosa para formar un aducto;

   b) una cantidad efectiva de un material adsorbente capaz de adsorber dicha sustancia gaseosa, y reduciendo o evitando de la formación de dicho aducto; y

   c) un paquete sellado que tiene un volumen incluido dentro del cual están situados el dispositivo y el material adsorbente;

   en donde el paquete sellado es sustancialmente impermeable a las sustancias gaseosas; y en donde la sustancia gaseosa es diferente al propulsor HFA (hidrofluoroalcano)

2. Un sistema de acuerdo a la reivindicación 1, en donde el material adsorbente está alojado en el dispositivo.

3. Un sistema de acuerdo a la reivindicación 1, en donde el paquete sellado es sustancialmente impermeable a la humedad.

4. Un sistema de acuerdo a una cualquiera de las reivindicaciones 1 a 3, en donde el dispositivo se selecciona de un grupo que consiste de una jeringa y un inhalador de polvo seco.

5. Un sistema de acuerdo a una cualquiera de las reivindicaciones 1 a 4, en donde el dispositivo es un inhalador de polvo seco.

6. Un sistema de acuerdo a una cualquiera de las reivindicaciones 1 a 5, en donde el medicamento es un medicamento antiinflamatorio usado en el tratamiento de una enfermedad respiratoria.

7. Un sistema de acuerdo a una cualquiera de las reivindicaciones 1 a 1 a 6, en donde el componente libera indeseablemente la sustancia gaseosa.

8. Un sistema de acuerdo a una cualquiera de las reivindicaciones 1 a 7, en donde el componente es un elemento plástico de un dispositivo de inhalador de polvo seco.

9. Un sistema de acuerdo a la reivindicación 8, en donde el elemento plástico comprende un material poliacetal.

10. Un sistema de acuerdo a una cualquiera de las reivindicaciones 1 a 9, en donde la sustancia gaseosa es formaldehído.

11. Un sistema de acuerdo a una cualquiera de las reivindicaciones 1 a 10, en donde el material adsorbente se incorpora en una mezcla de polímero y se manufactura en un componente plástico del dispositivo de médico.

12. Un sistema de acuerdo a una cualquiera de las reivindicaciones 1 a 10, en donde el material adsorbente se incorpora en una lámina plástica usada en el empaquetamiento del dispositivo.

13. Un sistema de acuerdo a una cualquiera de las reivindicaciones 1 a 10, en donde el material adsorbente se incorpora en un adhesivo (por ejemplo un parche o cinta autoadhesiva).

14. Un sistema de acuerdo a una cualquiera de las reivindicaciones 1 a 10, en donde el material adsorbente está en una bolsita porosa.

15. Un sistema de acuerdo a una cualquiera de las reivindicaciones 1 a 14, en donde el material adsorbente comprende material seleccionado del grupo que consiste de tamices moleculares, arcillas activadas, carbón vegetal, alúmina activada, sílice, zeolitas, bauxitas, y mezclas de éstos.

16. Un sistema de acuerdo a una cualquiera de las reivindicaciones 1 a 15, en donde el material adsorbente son tamices molecular de 10 Å (Ángstrom).

17. Un sistema de acuerdo a una cualquiera de las reivindicaciones 1 a 16, en donde el paquete está hecho de metal, vidrio, o plástico, y se selecciona del grupo que consiste de botellas, bolsas, cajas de tambor, y contenedores de forma irregular.

18. Un sistema de acuerdo a una cualquiera de las reivindicaciones 1 a 17, en donde el paquete está hecho de plástico.

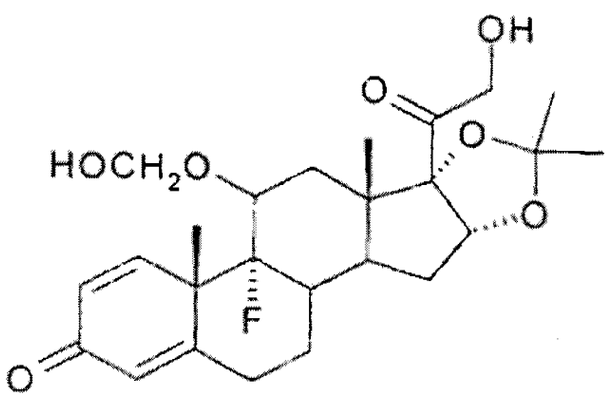
19. Un sistema de acuerdo a una cualquiera de las reivindicaciones 1 a 18, en donde el paquete es una lámina flexible que comprende tres capas: poliéster / aluminio / polietileno, en donde la capa de aluminio está entre las capas de poliéster y polietileno.

20. Un sistema de acuerdo a una cualquiera de las reivindicaciones 1 a 19, en donde el paquete está sellado herméticamente mediante sellado con calor, mediante pegamento, soldadura, soldadura fuerte, cerrados mecánicos o abrazaderas, o compresión.

21. Un sistema de acuerdo a una cualquiera de las reivindicaciones 1 a 20, en donde el medicamento es triamcinolona acetonida.

22. Un sistema de acuerdo a una cualquiera de las reivindicaciones 1 a 21, en donde el material adsorbente está en una cantidad suficiente para prevenir la formación de un aducto.

23. Un sistema de acuerdo a una cualquiera de las reivindicaciones 1 a 22, en donde el aducto es de la fórmula:



24. Un método para prevenir la formación de un aducto en un producto farmacéutico que comprende un dispositivo médico, dicho dispositivo comprende un medicamento y un componente que libera gradualmente una sustancia gaseosa diferente del propulsor HFA (hidrofluoroalcano), y una cantidad efectiva de dicho material absorbente capaz de adsorber dicha

sustancia gaseosa, dicha formación se debe a la reacción química entre el medicamento y dicha sustancia gaseosa

En donde el método comprende las etapas de:

(i) posicionar una cantidad efectiva de un material adsorbente y el dispositivo médico dentro de un paquete sellable que es sustancialmente impermeable a las sustancias gaseosas;

(ii) sellar el paquete para que el dispositivo médico y el adsorbente estén en un volumen envolvente dentro del paquete; y

(iii) adsorber cualquier escape de la sustancia gaseosa del componente para prevenir la formación de un aducto.

25. Un método de acuerdo a la reivindicación 24, en donde el material adsorbente está alojado en el dispositivo.

26. Un método de acuerdo a una cualquiera de las reivindicaciones 26 a 25, en donde el medicamento es un medicamento antiinflamatorio usado en el tratamiento de enfermedades respiratorias.

27. Un método de acuerdo a una cualquiera de las reivindicaciones 26 a 26, en donde la sustancia gaseosa es formaldehído.

28. Un método de acuerdo a una cualquiera de las reivindicaciones 26 a 27, en donde el material adsorbente se incorpora en una mezcla de polímero y se manufactura en un componente plástico del dispositivo médico.

29. Un método de acuerdo a una cualquiera de las reivindicaciones 26 a 27, en donde el material adsorbente se incorpora en una lámina plástica usada en el empaquetamiento del dispositivo.

30. Un método de acuerdo a una cualquiera de las reivindicaciones 26 a 27, en donde el material adsorbente se incorpora en un adhesivo (por ejemplo un parche o cinta autoadhesiva)

31. Un método de acuerdo a una cualquiera de las reivindicaciones 26 a 27, en donde el material adsorbente está en una bolsita porosa.

32. Un método de acuerdo a una cualquiera de las reivindicaciones 24 a 31, en donde el material adsorbente comprende material seleccionado del grupo que consiste de tamices moleculares, arcillas activadas, carbón vegetal, alúmina activada, sílice, zeolitas, bauxitas, y mezclas de éstos.

33. Un método de acuerdo a una cualquiera de las reivindicaciones 24 a 32, en donde el material adsorbente tamiz molecular de 10 Å (Ángstrom).

34. Un método de acuerdo a una cualquiera de las reivindicaciones 24 a 33, en donde el medicamento es triamcinolona acetonita,

35. Un método de acuerdo a una cualquiera de las reivindicaciones 24 a 32, en donde el material adsorbente está en una cantidad suficiente para prevenir la formación de un aducto.

US006179118B1

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

(10) **Patent No.: US 6,179,118 B1**
(45) **Date of Patent: *Jan. 30, 2001**

(54) **METHOD AND PACKAGE FOR STORING A PRESSURIZED CONTAINER CONTAINING A DRUG**

(75) Inventors: **Karl Andrew Garrill**, Hertford (GB); **Richard J. Haan**, Germantown, TN (US); **Craig Steven Herman**, Raleigh, NC (US); **Richard Ian Walker**, Hertford (GB)

(73) Assignee: **Glaxo Wellcome Inc.**, Research Triangle Park, NC (US)

(*) Notice: Under 35 U.S.C. 154(b), the term of this patent shall be extended for 0 days.

This patent is subject to a terminal disclaimer.

(21) Appl. No.: **09/290,351**

(22) Filed: **Apr. 12, 1999**

Related U.S. Application Data

(63) Continuation-in-part of application No. 09/216,183, filed on Dec. 18, 1998, now Pat. No. 6,119,853.

(51) **Int. Cl.**[7] **B65D 81/26**
(52) **U.S. Cl.** **206/204**; 206/438; 206/439
(58) **Field of Search** 53/400, 403, 428, 53/449, 461; 206/204, 363, 365, 438, 439, 484.1, 570; 383/113; 604/890.1

(56) **References Cited**

U.S. PATENT DOCUMENTS

3,788,322	*	1/1974	Michaels	128/260
3,797,492	*	3/1974	Place	128/260
4,135,622		1/1979	Glick .	
4,449,632	*	5/1984	Marusiak, Jr.	206/540
4,509,196	*	4/1985	Sak et al.	206/438
4,655,229		4/1987	Sensabaugh, Jr. et al. .	
4,702,963		10/1987	Phillips et al. .	
4,874,090	*	10/1989	Dyke	206/439
4,907,394		3/1990	Tschepke et al. .	
4,988,558		1/1991	Shigemoto .	
5,073,599		12/1991	Genske .	
5,322,161		6/1994	Shichman et al. .	
5,441,060		8/1995	Rose et al. .	
5,645,051		7/1997	Schultz et al. .	
5,687,746		11/1997	Rose et al. .	
5,718,355	*	2/1998	Garby et al.	206/459.1
5,746,227		5/1998	Rose et al. .	
5,756,171		5/1998	Moteki et al. .	
5,833,066	*	11/1998	Hargus et al.	206/438

FOREIGN PATENT DOCUMENTS

414536A2	8/1990	(EP) .
428380A1	11/1990	(EP) .

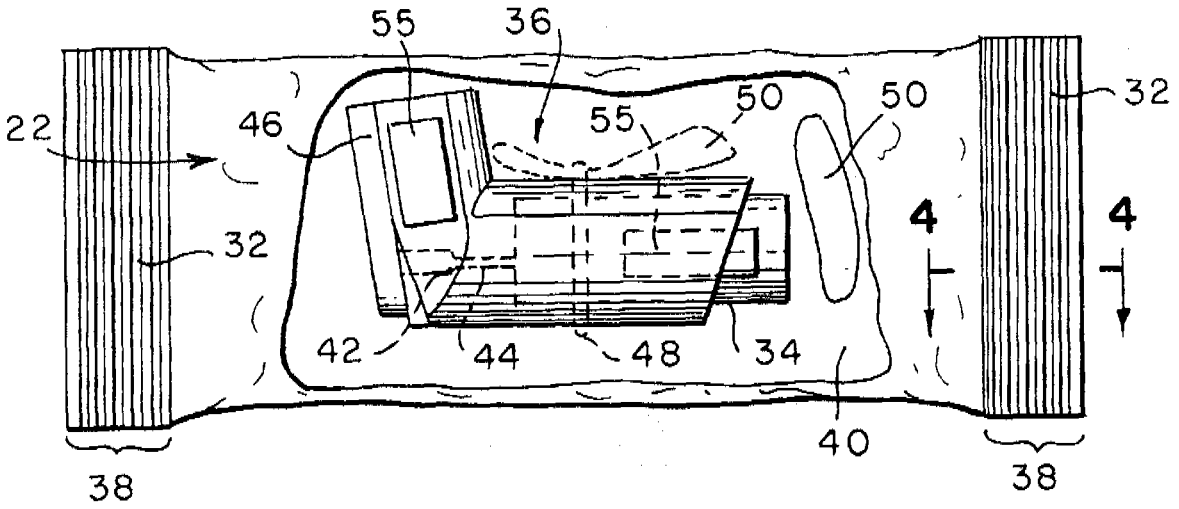
* cited by examiner

Primary Examiner—Jim Foster
(74) *Attorney, Agent, or Firm*—Christopher P. Rogers

(57) **ABSTRACT**

A method and package for storing a pressurized container which is filled with a drug formulation at a predetermined pressure. The drug formulation includes a mixture of a drug and a propellant. The package which encloses the pressurized container substantially prevents ingression of water vapor and particulate matter into the package while permitting egression of the propellant which may leak from the pressurized container.

26 Claims, 3 Drawing Sheets



METHOD AND PACKAGE FOR STORING A PRESSURIZED CONTAINER CONTAINING A DRUG

CROSS REFERENCE TO RELATED APPLICATIONS

This application is a continuation-in-part of U.S. application Ser. No. 09/216,183, U.S. Pat. No. 6,119,853, filed on Dec. 18, 1998, the entire contents of which are incorporated by reference.

BACKGROUND OF THE INVENTION

1. Field of the Invention

The present invention relates to a method and package for storing a pressurized container containing a drug.

2. Description of the Background Art

For environmental reasons, there has been a move to replace chlorofluorocarbons (CFCs) (also simply known as "fluorocarbons") such as P11, P114 and P12 with hydrofluoroalkane propellants such as HFA-134a and HFA-227. When these hydrofluoroalkane propellants are used as a propellant in a pressurized drug delivery system, various technical problems can occur with various drug formulations. Also, it is necessary to modify the construction of metered dose inhalers for optimum stability and aerosol formation.

One storing mechanism for a metered dose inhaler (MDI) uses a plastic tube which has a resealable lid to close the tube. The resealable lid for this tube employs a desiccant to absorb moisture present in the tube.

Such plastic tubes typically increase manufacturing cost and require complex and/or expensive manufacturing processes. Such tubes are frequently bulky in that they require a significant amount of storage space relative to the size of the container disposed within the plastic tube.

SUMMARY OF THE INVENTION

Accordingly, a need in the art exists for a method and package for storing a pressurized container filled with a propellant and a drug which substantially prevents ingression of water vapor and particulate matter into the storage package while permitting egression of the propellant to increase shelf life and performance of the drug and the propellant. Furthermore, a need exists in the art to provide a method and package for storing a pressurized container filled with a drug and a propellant which is cost effective and which does not require complex manufacturing processes and which in turn efficiently envelopes the container to maximize available storage space.

It is a primary object of the present invention to provide a method and package for storing a pressurized container, where the pressurized container is filled with a drug and a propellant and where the method and package substantially prevent ingression of water vapor and particulate matter into the package while permitting egression of the propellant whereby shelf life of the drug is prolonged and performance of the drug and the propellant are maintained or increased.

It is a further object of the present invention to provide a method and package for storing a pressurized container filled with a drug and a propellant where the method and package substantially absorb residual moisture in the package enclosing the pressurized container that is sometimes present on the outer surface of the pressurized container prior to sealing pressurized container within the package.

Another object of the present invention is to provide a method and package for storing a pressurized container including a drug and a propellant which substantially reduces manufacturing costs while substantially reducing the complexity of the manufacturing process of the package.

Another object of the present invention is to provide a method and package for storing a pressurized container having a drug and a propellant which is easily opened and readily disposable.

It is a further object of the present invention to provide a method and package for storing a pressurized container having a drug and a propellant, whereby the propellant preferably meets governmental guidelines which prohibit the use of CFCs.

Another object of the present invention is to provide a method and package for storing a pressurized container which includes a drug and a propellant that does not require complex mechanical devices to envelope or enclose the pressurized container while substantially reducing the amount of storage space needed for the pressurized container where the package substantially conforms to the shape of the pressurized container. The package is amorphous in shape due to the flexible materials from which it is made.

Another object of the present invention is to provide a method and package which form an enclosed volume that stores a pressurized container in a controlled environment where the pressurized container is isolated from harmful environmental conditions such as humidity, dust, light, and water vapor and other particulate matter.

Another object of the present invention is to provide and article of manufacture comprising an integral aerosol dispensing apparatus, a drug formulation, and a flexible package. It is further an object of the present invention to provide a drug formulation and carrier with packaging material having labeling and information relating to the composition contained therein and printed thereon. Additionally, a further object of the invention is to provide an article of manufacture having a brochure, report, notice, pamphlet, or leaflet containing product information.

These and other objects of the present invention are fulfilled by providing a container storage system comprising: a drug formulation comprising a mixture of a drug and a propellant; a pressurized container filled with the drug formulation at a predetermined pressure; and a flexible package for wrapping and sealing the pressurized container providing an enclosed volume in which the pressurized container is disposed, the flexible package being impermeable to water vapor and permeable to the propellant, the flexible package substantially preventing ingression of water vapor and particulate matter into the enclosed volume while permitting egression of the propellant.

In addition, these and other objects of the present invention are also accomplished by providing a method of storing a container comprising the steps of: providing a flexible package material, which is impermeable to water vapor and permeable to a propellant; filling a container with a drug formulation comprising a drug and the propellant at a predetermined pressure; wrapping the container with the flexible package material to form an enclosed volume in which the container is disposed therein; and sealing the flexible package which in turn closes said enclosed volume, the flexible package substantially preventing ingression of water vapor and particulate matter into the enclosed volume while permitting egression of the propellant from the enclosed volume.

Moreover, these and other objects of the present invention are fulfilled by a packaged metered dose inhaler comprising:

an MDI comprising a container and a drug metering valve, a pressurized drug formulation in the container comprising a propellant and a drug dispersed or dissolved in the propellant; and an overwrap of flexible material enclosing said MDI, the overwrap being made of a moisture impermeable material.

Also, these and other objects of present invention are accomplished by providing an article of manufacture comprising: an aerosol dispensing apparatus for dispensing metered amounts of fluid material from a reservoir, the apparatus comprising a container defining a reservoir, a dispensing valve, a drug formulation located within the aerosol dispensing apparatus comprising a safe and effective medicament and a pharmaceutically acceptable propellant; and a flexible package for wrapping and sealing the container providing an enclosed volume in which said pressurized container is disposed, the flexible package being substantially impermeable to water vapor and permeable to the propellant, the flexible package substantially preventing ingression of water vapor and particulate matter into the enclosed volume while permitting egression of the propellant.

These and other objects of the present invention are also accomplished by providing a method of improving a product performance comprising the steps of: providing a flexible package material made of at least one heat sealable layer, at least one layer of a metal foil, and a protective layer; the flexible package material being impermeable to water vapor and permeable to a propellant; filling a container with a drug formulation comprising a drug and the propellant at a predetermined pressure; wrapping the container with the flexible package material to form an enclosed volume in which the container is disposed therein; and sealing the flexible package which in turn closes the enclosed volume, the flexible package substantially preventing ingression of water vapor and particulate matter into the enclosed volume while permitting egression of the propellant from the enclosed volume.

Further scope of applicability of the present invention will become apparent from the detailed description given hereinafter. However, it should be understood that the detailed description and specific examples, while indicating preferred embodiments of the invention, are given by way of illustration only, since various changes and modifications within the spirit and scope of the invention will become apparent to those skilled in the art from this detailed description.

BRIEF DESCRIPTION OF THE DRAWINGS

The present invention will become more fully understood from the detailed description given hereinbelow and the accompanying drawings which are given by way of illustration only, and thus are not limitative of the present invention, and wherein:

FIG. 1 is a top elevational view of the package for storing a pressurized container of the present invention;

FIG. 2 is a side view of the package for storing a pressurized container of the present invention;

FIG. 3 is a cutaway bottom view of the package for storing a pressurized container of the present invention;

FIG. 4 is a cross-sectional view of the package for storing a pressurized container of the present invention;

FIG. 5 is a cross sectional view of a metering valve which could be used in the present invention; and

FIG. 6 is a side view of the second container with a product label which is placed over the wrapping means of the present invention.

DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENTS

Pressurized Containers

The pressurized containers useful in the invention include any containers in which a drug and a propellant can be stored. Slow leakage of propellant sometimes occurs in metered dose inhalers (MDIs) and the present invention is particularly useful in connection with MDIs that may have slow leaks.

The pressurized container is preferably an MDI or an MDI can The term "metered dose inhaler" or "MDI" means a unit comprising a can, a crimped cap covering the mouth of the can, and a drug metering valve situated in the cap, while the term "MDI system" also includes a suitable channeling device. The term "MDI can" means the container without the cap and valve. The term "drug metering valve" or "MDI valve" refers to a valve and its associated mechanisms which delivers a predetermined amount of drug formulation from an MDI upon each activation. The channeling device may comprise, for example, an actuating device for the valve and a cylindrical or cone-like passage through which medicament may be delivered from the filled MDI can via the MDI valve to the nose or mouth of a patient, e.g. a mouthpiece actuator. The relation of the parts of a typical MDI is illustrated in U.S. Pat. No. 5,261,538 incorporated herein by reference. An exemplary MDI is disclosed in WO 96/26755, the entire contents of which is hereby incorporated by reference. Other exemplary pressurized containers for use in MDIs are disclosed in WO 96/32151, WO 96/32345, WO 96/32150 and WO 96/32099.

The pressurized container 34 is preferably a vial made from aluminum. However, other materials are not beyond the scope of the present invention. Other materials for the pressurized container 34 include, but are not limited to, ferrous alloys, non-ferrous alloys, such as stainless steel, ceramic materials, polymers, composite materials, and mixtures thereof. Suitable containers which contain a polymeric coating on the inside thereof are disclosed in WO 96/32151.

Most often the MDI can and cap are made of aluminum or an alloy of aluminum, although other metals not affected by the drug formulation, such as stainless steel, an alloy of copper or tin plate, may be used. An MDI can may also be fabricated from glass or plastic. Preferably, however, the MDI cans employed in the present invention are made of aluminum or an alloy thereof. Advantageously, strengthened aluminum or aluminum alloy MDI cans may be employed. Such strengthened MDI cans are capable of withstanding particularly stressful coating and curing conditions, e.g., particularly high temperatures, which may be required for certain fluorocarbon polymers. Strengthened MDI cans which have a reduced tendency to misform under high temperatures include MDI cans comprising side walls and a base of increased thickness and MDI cans comprising a substantially ellipsoidal base (which increases the angle between the side walls and the base of the can), rather than the hemispherical base of standard MDI cans. MDI cans having an ellipsoidal base offer the further advantage of facilitating the coating process.

The MDI cans include MDI cans supplied by Presspart of Cary, N.C., USA or the United Kingdom, or by Neotechnic of the United Kingdom. The MDI cans typically have a neck diameter of 20 millimeters, although any suitable neck diameter may be used and can vary in height from 30 millimeters to 60 millimeters.

The drug metering valve consists of parts usually made of stainless steel, a pharmacologically inert and propellant resistant polymer, such as acetal (polyoxymethylene), polya-

Table 5
Permeate characteristics: clarified juice feed

Property	Permionics	
	60 mil	80 mil
Average flux[a] (LMH)	31.53	21.64
Purity rise	2.10	1.48
Brix rejection (%)	11.47	4.64
Non-sugars rejection (%)	19.01	11.05
Sugar rejection (%)	9.00	2.91

[a] Averaged over five experiments.

4. Conclusions

This work presents an on-site assessment of polymeric spiral wound modules for sugarcane juice UF. The variation in flux and juice properties with varying parameters like module channel height, transmembrane pressure and feed temperature were investigated on the raw juice and clarified juice streams. The main points that emerged from this study are listed below:

- UF produces a permeate that is consistently superior in terms of lower color, higher clarity and lower CaO content as compared to the clarified juice obtained by the conventional liming-sulphitation process.
- The average purity rise across UF was greater than 2 units with raw juice feed and over 1.5 units with clarified juice feed. These values are a significant improvement over the 0.5–1 unit purity rise obtained in the conventional clarification scheme.
- Both the raw juice and clarified juice streams were characterized by the presence of bagacillo fines which could not be eliminated by prefiltration through sieves up to 150 mesh. These fines have a tendency to deposit upon the membrane surface during the course of UF thus creating a secondary layer that eventually controls the juice filtration characteristics.
- A combination of narrow channel height at low operating pressure is likely to result in a satisfactory flux, particularly during long-term operation.
- Among the modules tested, the Permionics spirals with low channel heights (40 or 60 mil channel spacers) appear to be the best choice in terms of both higher flux and improvement in juice color.

Acknowledgements

This work was supported by a grant from the Sugar Technology Mission, Technology Information Forecasting and Assessment Council, Department of Science and Technology, Government of India. We deeply appreciate the support and co-operation provided by The Simbhaoli Sugar Mills Ltd., Simbhaoli, while performing the trials at their factory. We particularly thank Mr. S.N. Misra, Mr. N.C. Sharma and Mr. Ranga Rao for useful discussions and suggestions. The membrane modules provided by Mr. S.J. Mayor, Permionics and Dr. F. Müller, Inchema Consulting AG are also gratefully acknowledged.

References

[1] M. Balakrishnan, M. Dua, J.J. Bhagat, Evaluation of ultrafiltration for juice purification in plantation white sugar manufacture, Int. Sugar J. 1213 (2000) 21.
[2] R.F. Madsen, Application of ultrafiltration and reverse osmosis to cane juice, Int. Sugar J. 75 (894) (1973) 163.
[3] S. Kishihara, S. Fujii, M. Komoto, Ultrafiltration of cane juice: influence of flux and quality of permeate, Int. Sugar J. 83 (1981) 35.
[4] S. Kishihara, S. Fujii, M. Komoto, Improvement of flux in ultrafiltration of cane juice, Int. Sugar J. 85 (1983) 99.
[5] W.K. Nielsen, S. Kristensen, R.F. Madsen, Prospects and possibilities in application of membrane filtration systems within the beet and cane sugar industry, Sugar Technol. Rev. 9 (1982) 59.
[6] T. Masakuni, N. Sanehisa, Membrane permeability of cane juice on ultrafiltration with several kinds of membrane, Agric. Biol. Chem. 50 (4) (1986) 833.
[7] S. Kishihara, H. Tamaki, S. Fujii, M. Komoto, Clarification of technical sugar solutions through a dynamic membrane formed on a porous ceramic tube, J. Membr. Sci. 41 (1989) 103.
[8] S.K. Verma, R. Srikanth, S.K. Das, G. Venkidachalam, An efficient and novel approach for clarification of sugarcane juice by micro- and ultrafiltration methods, Ind. J. Chem. Technol. 3 (3) (1996) 136.
[9] R.J. Kwok, 55th Annual Sugar Industry Technologists Meeting, Durban, SA, 1996.
[10] S. Cartier, M. Theoleyre, X. Lancrenon, M. Decloux, Membrane technology in the sugar industry, in: Proceedings of the Sugar Processing Research Institute Workshop on Separation Processes in the Sugar Industry, New Orleans, Louisiana, USA, 1996, pp. 55–68.
[11] C.C. Willet, The A.B.C. process. Direct production of refined quality sugar from cane mixed juice, Int. Sugar J. 99 (1177E) (1997) 7.
[12] M. Saska, J. McArdle, A. Eringis, Filtration of clarified cane juice using spiral polymeric membrane configuration,

made (e.g., Nylon®), polycarbonate, polyester, fluorocarbon polymer (e.g., Teflon®) or a combination of these materials. Additionally, seals and "O" rings of various materials (e.g., nitrile rubbers, polyurethane, acetyl resin, fluorocarbon polymers), or other elastomeric materials are employed in and around the valve.

The preferred MDI valves have typical metering chamber volumes of 25 to 63 microliters. The valves preferably have a ferrule skirt to suit a 20 mm neck diameter can. Typical suppliers of MDI valves include Valois Pharm, France; Bespak of Europe or the United Kingdom, or Neotechnic, United Kingdom.

Drugs

Preferred drugs (also referred to as "medicaments") and drug combinations are disclosed in WO 98/32151, WO 96/32345, WO 96/32150 and WO 96/32099, the entire contents of which are hereby incorporated by reference. These drugs include, for example, fluticasone propionate or a physiologically acceptable solvate thereof, beclomethasone dipropionate or a physiologically acceptable solvate thereof, salmeterol or a physiologically acceptable salt thereof and albuterol or a physiologically acceptable salt thereof. Medicaments may be selected from, for example, analgesics, e.g. codeine, dihydromorphine, ergotamine, fentanyl or morphine; anginal preparations, e.g. diltiazem; antiallergics, e.g. cromoglycate, ketotifen or nedocromil; antiinfectives e.g. cephalosporins, penicillins, streptomycin, sulphonamides, tetracyclines and pentamidine; antihistamines, e.g. methapyrilene; anti-inflammatories, e.g. beclomethasone (e.g. the dipropionate), flunisolide, budesonide, tipredane or **triamcinolone acetonide**; antitussives, e.g. noscapine; bronchodilators, e.g. salbutamol, salmeterol, ephedrine, adrenaline, fenoterol, formoterol, isoprenaline, metaproterenol, phenylephrine, phenylpropanolamine, pirbuterol, reproterol, rimiterol, terbutaline, isoetharine, tulobuterol, orciprenaline, or (-)-4-amino-3,5-dichloro-α-[[[6-[2-(2-pyridinyl)ethoxy]hexyl]-amino]-methyl]benzenemethanol; diuretics, e.g. amiloride; anticholinergics e.g. ipratropium, atropine or oxitropium; hormones, e.g. cortisone, hydrocortisone or prednisolone; xanthines e.g. aminophylline, choline theophyllinate, lysine theophyllinate or theophylline; and therapeutic proteins and peptides, e.g. insulin or glucagon. It will be clear to a person skilled in the art that, where appropriate, the medicaments may be used in the form of salts (e.g. as alkali metal or amine salts or as acid addition salts) or as esters (e.g. lower alkyl esters) or as solvates (e.g. hydrates) to optimise the activity and/or stability of the medicament and/or to minimize the solubility of the medicament in the propellant.

Additionally, any suitable combination of drugs can be used in the present invention. For example, Seretide (fluticasone and Serevent) can be used in the present invention.

Propellants

"Propellants" used herein mean pharmacologically inert liquids with boiling points from about room temperature (25° C.) to about −25° C. which singly or in combination exert a high vapor pressure at room temperature, including CFCs such as Freon and hydrofluorocarbons. Upon activation of the MDI system, the high vapor pressure of the propellant in the MDI forces a metered amount of drug formulation out through the metering valve then the propellant very rapidly vaporizes dispersing the drug particles. The propellants used in the present invention are low boiling fluorocarbons; in particular, hydrofluorocarbons or hydrofluoroalkanes such as HFA-134a and HFA-227. The invention is particularly useful with propellants (including propellant mixtures) which are more hygroscopic than P11, P114 and/or P12 such as HFA-134a and HFA-227.

Additional Components of the Drug Formulation

The MDIs taught herein are particularly useful for containing and dispensing inhaled drug formulations with hydrofluoroalkane propellants such as 134a with little, or essentially no, excipient and which tend to deposit or cling to the interior walls and parts of the MDI system. In certain cases, it is advantageous to dispense an inhalation drug with essentially no excipient, e.g., where the patient may be allergic to an excipient or the drug reacts with an excipient.

Drug formulations for use in the invention may be free or substantially free of formulation excipients, e.g., surfactants and cosolvents, etc. Such drug formulations are advantageous since they may be substantially taste and odor free, less irritant and less toxic than excipient-containing formulations. Thus, a preferred drug formulation consists essentially of a drug, or a physiologically acceptable salt or solvate thereof, optionally in combination with one or more other pharmacologically active agent, and a fluorocarbon propellant.

Further drug formulations for use in the invention may be free or substantially free of surfactant. Thus, a further preferred drug formulation comprises or consists essentially of a drug (or a physiologically acceptable salt or solvate thereof), optionally in combination with one or more other pharmacologically active agents, a fluorocarbon propellant and 0.01 to 5% w/w based on the propellant of a polar cosolvent, which formulation is substantially free of surfactant. Preferred propellants are 1,1,1,2-tetrafluoroethane, 1,1,1,2,3,3,3-heptafluoro-n-propane or mixtures thereof, and especially 1,1,1,2-tetrafluoroethane or 1,1,1,2,3,3,3-heptafluoro-n-propane. However, the drug formulation may contain any additional excipients which are necessary or desirable to prepare a suitable drug formulation.

The term "excipients" as used herein means chemical agents having little or no pharmacological activity (for the quantities used) but which enhance the drug formulation or the performance of the MDI system. For example, excipients include but are not limited to surfactants, preservatives, flavorings, antioxidants, antiaggregating agents, and cosolvents, e.g., ethanol and diethyl ether.

Suitable surfactants are generally known in the art, for example, those surfactants disclosed in European Patent Application No. 0327777. The amount of surfactant employed is desirably in the range of 0.0001% to 50% w/w ratio relative to the drug, in particular 0.05 to 5% w/w ratio.

A polar cosolvent such as C_{2-6} aliphatic alcohols and polyols, e.g., glycerol, ethanol, isopropanol and propylene glycol, preferably ethanol, may be included in the drug formulation in the desired amount, either as the only excipient or in addition to other excipients, such as surfactants. Suitably, the drug formulation may contain 0.01 to 5% w/w based on the propellant of a polar cosolvent, e.g., ethanol, preferably 0.1 to 5% w/w, e.g., about 0.1 to 1% w/w.

Flexible Packaging Materials

The flexible packaging material can be any material which is impervious to or substantially impervious to moisture. The packaging material is preferably permeable to propellants such as HFA-134a and/or HFA-227 whereby if the propellant slowly leaks from the pressurized container, the propellant will slowly pass, by diffusion or otherwise, through the packaging material.

For ease of manufacturing, and in order to provide the necessary properties to the packaging material, the flexible packaging material preferably comprises a non-thermoplastic substrate (such as a metal foil) and [redacted]

[redacted] disposed thereon, and an additional protective layer, such as a polymer film of polyester. The heat sealable layer is usually disposed on the inner surface of the assembled package. The additional protective layer is usually disposed on the surface opposite the heat sealable layer. An example of a particularly useful foil laminate is a polyester film adhesively laminated to aluminum foil adhesively laminated to Ionomer (SURLYN™) film, for example, 12μ polyester/9μ aluminum/50μ ionomer film supplied by Lawson Mardon Singen (LMS).

The substrate is preferably formed from aluminum foil. However, other metals for the substrate include, but are not limited to, tin, iron, zinc, or magnesium formed on a sheet by vacuum deposition or sputtering and a carboxyl group-containing polyolefin layer formed on the metal layer by lamination.

The heat sealable layer can be formed from any thermoplastic or thermosetting material such as an ionomer resin, polyolefin, or cycloolefin copolymer. Ionomer resins typically include ionically cross-linked ethylene-methacrylic acid and ethylene acrylic acid copolymers. Properties which distinguish these ionomers resins from other polyolefin heat-sealed polymers are high clarity, high impact resistance, low haze in lamination, tear resistance, abrasion resistance, solid state toughness, and moisture imperviousness. In the preferred embodiment, the heat sealable layer is made out of SURLYN™ (an ionomer resin) or a form of polyethylene to provide sufficient heat sealing properties.

The outer protective layer, if present, can be formed of any material as long as the final laminate has the requisite properties.

Preferably, the protective layer (e.g., polyester) is adhesively laminated to the substrate (e.g., aluminum) and the substrate layer in turn is adhesively laminated to the heat sealable layer (e.g., the ionomer film or SURLYN™ (an ionomer resin)).

Preferred exemplary thicknesses of the three layers include a protective layer 1 to 40, preferably 4 to 30, more preferably 10 to 23 microns, and most preferably 12 microns; a substrate layer of 1 to 100, preferably 3 to 70, more preferably 5 to 50 microns, more preferably 6 to 20 microns, and most preferably 9 microns. For the heat sealable layer, preferred exemplary thicknesses include thicknesses of 1 to 100, preferably 5 to 70, more preferably 10 to 60, more preferably 20 to 55 microns, and most preferably 50 microns.

Adhesives may be used to join the respective layers of materials together. The adhesive layers are typically substantially smaller in thickness relative to the thickness of the substrate, heat sealable and/or protective layers which they bond.

The number, size, and shape of the layers are not limited to those layers shown in the drawings. Any number of layers with relative areas of any size and predetermined thicknesses may be used so long as the [redacted] forms an enclosed volume which substantially prevents ingression of [redacted] into the enclosed volume while [redacted] out of the enclosed volume of any propellant leaving the pressurized container. The size, shape, and number of layers of the package is typically a function of the size and contents of the pressurized container which includes a drug and a propellant.

The package is believed to operate similarly to a virtual one-way valve due to the composition of the layers and due to the transmission rate of water vapor molecules into the enclosed volume relative to the transmission rate of gas molecules of a [redacted], such as [redacted], out of the enclosed volume. The package permits the propellant in the pressurized container to diffuse out of the enclosed volume while substantially preventing water vapor and other particulate matter from entering the enclosed volume. Excess or leakage of the propellant is permitted to egress from the package. The virtual one-way valve function of the package prevents or minimizes the chance of any sudden ruptures or prevents or minimizes unexpected expulsion of the propellant during opening of the package.

Moisture Absorbing Materials

The moisture absorbing material is preferably a silica gel desiccant packet. However, other vapor or moisture absorbing mechanisms are not beyond the scope of the present invention. Other vapor or moisture absorbing materials include desiccants made from inorganic materials such as [redacted] and alumina. Such inorganic materials of vapor or moisture absorbing materials have high water absorption capacities and favorable water absorption isotherm shapes. The water absorption capacity of such materials typically varies from 20 to 50 weight percent.

In the preferred embodiment, the absorbing material is a INIPAX® supplied by Multisorb Technologies in the United States and Silgelac in Europe (silica gel packaged inside TYVEK®, which is a nylon mesh bonded with a microporous polyurethane). Other exemplary moisture absorbing materials include, but are not limited to, alumina, **bauxite, anhydrous, calcium sulfate, water absorbing clay, activated bentonite clay, a molecular sieve, or** other like Materials which optionally include a moisture sensitive color indicator such as cobalt chloride to indicate when the desiccant is no longer operable. While in the preferred embodiment of the present invention, the package is designed to substantially prevent ingression of water vapor and particulate matter into the enclosed volume, the moisture absorbing material is placed within the enclosed volume in order to absorb any residual moisture present in the atmosphere or on the external surface of the pressurized container or mouthpiece or a combination thereof, prior to sealing the package.

The desiccant should be present in an amount sufficient to absorb any residual moisture inside the package or which might escape from inside the pressurized container. When silica gel is used, 1 g to 10 g of silica gel is sufficient for a typical MDI. Moreover, the desiccant should be present in an amount sufficient to absorb any moisture that possibly ingresses from the external environment.

It is also possible to place the desiccant inside the container, either loose in the canister or as part of an assembly attached to the canister.

The Container Storage System

Referring in detail to the drawings and with particular reference to FIG. **1**, a container storage system (or packaged product) **20** is shown. The container storage system **20** includes a **package or wrapping 22** that employs multi-layers of material **24**, **26**, **28**. (See FIG. 4.) The package **22** further includes fin seams **30**, **32** which are disposed along two parallel side edges of the package and along a single longitudinal edge of the package **22**.

The number and type of fin seams **30**, **32** are not limited to the types shown in the drawings. The package **22** can include additional seams or significantly fewer seams such as a continuous single seam. The orientation of the seams **30**, **32** is not limited to the orientation shown in the drawings. The orientation of the seams **30**, **32** is typically a function of the sealing device and such seams may be oriented in a manner which substantially increases manufacturing efficiency. During manufacture, the longitudinal seam **30** may

LAS METAS

Los japoneses siempre han gustado del pescado fresco. Pero las aguas cercanas a Japón no han tenido muchos peces por décadas.

Así que para alimentar a la población japonesa, los barcos pesqueros fueron fabricados más grandes para ir mar adentro.

Mientras más lejos iban los pescadores más era el tiempo que les tomaba regresar a entregar el pescado.

Si el viaje tomaba varios días, el pescado ya no estaba fresco.

Para resolver el problema, las compañías instalaron congeladores en los barcos pesqueros.

Así podían pescar y poner los pescados en los congeladores.

Sin embargo, los japoneses pudieron percibir la diferencia entre el pescado congelado y el fresco y no les gustaba el congelado, que, por lo tanto, se tenía que vender más barato.

Las compañías instalaron entonces en los barcos tanques para los peces.

Podían así pescar los peces, meterlos en los tanques y mantenerlos vivos hasta llegar a la costa. Pero después de un tiempo los peces dejaban de moverse en el tanque. Estaban aburridos y cansados, aunque vivos. Los consumidores japoneses también notaron la diferencia del sabor porque cuando los peces dejan de moverse por días, pierden el sabor fresco ....

y ¿cómo resolvieron el problema las compañías japonesas?

Y ¿cómo consiguieron traer pescado con sabor de pescado fresco?

Si las compañías japonesas te pidieran asesoría, ¿qué les recomendarías?

(Mientras piensas en la solución.... Lee lo que sigue):

Tan pronto una persona alcanza sus metas, tales como empezar una nueva empresa, pagar sus deudas, encontrar una pareja maravillosa, o lo que sea, empieza a perder la pasión. Ya no necesitará esforzarse tanto. Así que solo se relaja.

...n, the shape of the package may conform to some ...the internal shape of the rigid container if the ...the rigid container is just slightly larger than the ...volume of the flexible package.

...exemplary embodiment, FIG. 3 shows the pres... ...ntainer 34 to be connected to a nozzle 42 by a ...44. The pressurized container 34 is preferably an ...n metal vial having a metering valve 60 (See FIG. ...d therein which is connected to the valve stem 44. ...rized container 34 is not limited to the nozzle 42 ...stem 44 shown and the metering valve 60. While ...ized container 34 preferably includes a metering ...er valve systems are not beyond the scope of the ...invention. Other valve systems include, but are not limited to, wedge gate valve systems, double-disc gate valve systems, globe and angle valve systems, swing check valve systems, end cock valve systems, and other like valve systems. Since the pressurized container 34 is preferably part of an MDI, the valve design is typically a function of providing a predetermined dosage or amount of the drug contained within the pressurized container 34 to a user.

The nozzle 42 is typically fixably secured to the mouthpiece 46. However, other embodiments where the nozzle 42 is separate or detached from the mouthpiece 46 is not beyond the scope of the present invention. The pressurized canister 34, the nozzle 42, and the mouthpiece 46 together comprise an MDI 36.

As seen in FIG. 3, nozzle 42 is in fluid communication with the mouthpiece 46 so that upon movement of the pressurized container relative to the mouthpiece 46 in a direction where the pressurized container 34 moves towards the nozzle 42 fixed to one side of the mouthpiece 46, a metered dosage or predetermined amount of the drug and propellant contained within the pressurized container 34 is released. Such a combination of the fixed nozzle 42, mouthpiece 46, valve stem 44, and pressurized container 34 form an MDI 36 as outlined above.

The MDI 36 can be packaged by the flexible packaging material 22 in either an assembled state (valve stem 44 fixed to nozzle 42) or a disassembled state (valve stem 44 detached from nozzle 42). In a preferred embodiment, the **moisture absorbing material 50 lays adjacent to the mouthpiece 46** in a loose or free flowing manner. Alternatively, the moisture absorbing material can be secured to the inside of the flexible package. In another alternative embodiment, the moisture absorbing material may be disposed within the container 34 or attached to a bracket structure such as a ring which is fastened to the container 34.

In one possible embodiment, the moisture absorbing material may be attached to the external surface of the mouthpiece 46 by a fastening device such as a rubber band 48. The fastening device 48 is preferably a removable elastic mechanism such as a rubber band. However, other fastening devices are not beyond the scope of the present invention. Other fastening devices include, but are not limited to, adhesives, adhesive tapes, shrink-wrap plastic, fasteners such as screws, nails, or rivets, compartments which are part of the mouthpiece housing 46, and other like attachment devices.

The mouthpiece 46 substantially encloses pressurized container 34. The mouthpiece 46 is preferably simple in structure so that manufacturing efficiency and economy is substantially increased. However, other mouthpieces 46 are not beyond the scope of the present invention. Other mouthpieces include, but are not limited to, relatively movable mouthpieces with multiple parts, mouthpieces which also include a protective casing substantially surrounding the mouthpiece protecting the mouthpiece 46 from damage due to shock, and other like mouthpiece structures.

The pressurized container 34 may be held in the mouthpiece 46 by ribs or projections (not shown) extending from walls of the mouthpiece so that the pressurized container 34 is in a press-fit engagement with the mouthpiece 46. The valve stem 44 also provides a secure connection to the nozzle 42 which is fixedly secured to the mouthpiece 46. Other types of supporting mechanisms which hold the pressurized container 34 within the mouthpiece 46 are not beyond the scope of the present invention. Other types of securing or supporting mechanisms include, but are not limited to, fasteners such a screws, nails, or rivets, adhesives, mouthpieces with a female or male locking/keying mechanism which engages with a predetermined shape of the pressurized container, or other like supporting structures.

In the preferred embodiment of the invention, the support mechanisms, such as ribs or projections (not shown) of the mouthpiece 46 are designed for manufacturing efficiency which in turn reduces cost of the overall manufacturing process of the mouthpiece 46. The mouthpiece 46 is preferably made of plastic, however other materials are not beyond the scope of the present invention. Other materials for the mouthpiece 46 include, but are not limited to, ferrous alloys, non-ferrous alloys, ceramic materials, and composite materials and any mixtures thereof. Similar to the mouthpiece, the valve stem 44 is preferably made of plastic, but other materials are not beyond the scope of the present invention. Other materials for the valve stem 44 include, but are not limited to, ferrous alloys, non-ferrous alloys, ceramic materials, composite materials, and any mixtures thereof.

The pressurized container 34 preferably includes a liquid stored within the pressurized container 34 at a predetermined pressure. **The liquid preferably includes a drug dispersed or dissolved therein such as salmeterol or fluticasone propionate.**

In FIG. 4, a cross-sectional view of the package 22 is shown. Fin seams 32 include two peripheral edges 52, 54 of the flexible packaging material. [redacted] comprising a first layer 24, a second layer 26 and a [redacted] layer 28 as depicted. The first layer 24 and third layer 28 are preferably made from polymers. The first layer 24 is preferably made out of polyester while the third layer 28 is preferably made out an ionomer resin. The second layer 26 is preferably made of a metal foil. In the preferred embodiment, the metal foil is made of aluminum. In an alternative embodiment, the heat sealable layer is a polyethylene film.

As stated above, preferably, the protective layer (e.g., polyester) is adhesively laminated to the substrate (e.g., aluminum) and the substrate layer in turn is adhesively laminated to the heat sealable layer (e.g., the ionomer film or SURLYN™ (an ionomer resin)) or [redacted]

Preferred exemplary thicknesses of the three layers include a protective layer made of a polyester film having a thickness of 1 to 40, preferably 4 to 30, more preferably 10 to 23 microns, and most preferably 12 microns; a substrate layer made of aluminum having a thickness of 1 to 100, preferably 3 to 70, more preferably 5 to 50 microns, more preferably 6 to 20 microns, and most preferably 9 microns. For the heat sealable layer, an ionomer film is used having a preferred exemplary thicknesses of 1 to 100, preferably 5 to 70, more preferably 10-60, more preferably 25-55 microns, and most preferably 50 microns. In an alternative embodiment, a heat sealable layer of polyethylene film is used having a preferred thicknesses of 1 to 100, preferably 5 to 70, more preferably 10–60, more preferably 20–50 microns, and most preferably 50 microns.

Preferred exemplary embodiments include a polyester film as the protective layer having a thickness ranging from 12 to 23 microns. The polyester film is laminated to an aluminum foil as the substrate layer having a thickness ranging from 6 to 20 microns. The aluminum foil is laminated to a sealing film such as either an ionomer film having a thickness ranging from 25 to 50 microns or a polyethylene film having a thickness ranging from 20 to 50 microns.

Alternative preferred embodiments include aluminum metalized polyester film laminated to a heat sealable layer as outlined above. Another embodiment includes a silicon oxide coplated polyester film laminated to a heat sealable layer as outlined above. Yet, in another embodiment, a polyester film as a protective layer having a thickness ranging from 12 to 30 microns is laminated to an aluminum foil substrate layer having a thickness ranging from 6 to 20 microns, the aluminum foil being laminated to a polyester film of 12 to 30 microns which is laminated to a heat sealable layer as outlined above. In another embodiment, a polypropylene film as a protective layer having a thickness ranging from 15 to 30 microns is laminated to an aluminum foil substrate layer having a thickness ranging from 6 to 20 microns, and the aluminum foil is laminated to a heat sealable layer as outlined above. The laminates of the present invention can be adhesively laminated or extrusion laminated.

The general structure for the preferred embodiment of the present invention is as follows: OUTSIDE ENVIRONMENT, POLYESTER FILM 24, ALUMINUM FOIL 26, IONOMER FILM 28, ENCLOSED VOLUME 40, IONOMER FILM 28, ALUMINUM FOIL 26, POLYESTER FILM 24, OUTSIDE ENVIRONMENT. (See FIG. 4.)

The lines in the drawings which show the boundaries between respective layers 24, 26, and 28 may be considered as adhesive layers if adhesives are used to join the respective layers. In other words, for example, the line separating protective layer 24 from the metal foil layer 26 may be interpreted as an adhesive, if an adhesive is used to join these layers 24, 26.

FIG. 5 shows an exemplary fluid dispensing apparatus 36 containing a metered aerosol dispensing valve 60 which dispenses metered amounts of fluid material 76 from a reservoir 64. The fluid dispensing apparatus (or metered dose inhaler) may also be packaged as an article of manufacture (shown in FIGS. 2, 3, or 6) comprising an aerosol dispensing valve 60 of the present invention, an integral or additional dispensing apparatus, and a safe and therapeutically effective amount of a medicament in a pharmaceutically acceptable carrier, particularly a propellant. The medicament and carrier can also contain other medications and various excipients.

The packaging material of the article of manufacture may also have labeling 55 and information relating to the composition contained therein and/or printed thereon, such as by an adhesive label secured to the exterior of the flexible package. Additionally or alternatively, the article of manufacture of the present invention may have a brochure, report, notice, pamphlet, or leaflet 65 containing product information. This form of product information is sometimes, in the pharmaceutical industry, called the "package insert." A package insert 65 may be attached to or included with the article of manufacture. The package insert will usually be provided inside the box 74 but outside the flexible package. The package insert 65 and any article of manufacture labeling provides information relating to the composition

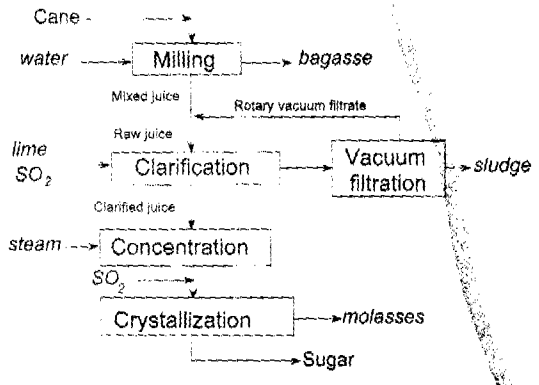


Fig. 1. Schematic of plantation white sugar manufacture.

Two feed streams in the manufacturing process (Fig. 1) viz. raw juice and clarified juice were studied. The effects of module channel height, operating pressure, operating time and feed temperature on juice flux and purity were examined. This data is expected to aid in the subsequent design of an UF demonstration plant with a juice handling capacity of 10 m^3/h.

2. Experimental

2.1. Membranes

Table 1 lists the spiral wound membrane modules that were evaluated for the treatment of sugarcane juice. The Cellpore® module was supplied by Inchema Consulting AG, Zurich, Switzerland. The remaining modules were obtained from Permionics, Vadodara, India. All the modules were commercially available and used without further modification except where specifically mentioned otherwise.

2.2. Ultrafiltration (UF) runs

The trials were performed on-site at the Simbhaoli Sugar Mills Ltd. which is located about 100 km from Delhi at Simbhaoli village, Ghaziabad district (Uttar Pradesh). The investigations spanned two cane crushing seasons between November 1997 and May 1999.

All experiments were conducted with fresh juice collected from the selected stage in the sugar manufacturing process. The feed was pre-treated appropriately and thereafter filtered through a combination of stainless steel (SS) screens to remove suspended particles. The pre-filtered feed (80–100 l) was then pumped through a fixed speed plunger pump (American Spring and Pressing Works Ltd., Mumbai, India) to the single spiral element. Depending upon the channel size, the effective filtration area varied in the 1–2.2 m^2 range. No temperature control was attempted for the feed though the feed temperature was monitored over the course of the experiments.

The UF was typically performed in a batch mode either with full retentate recycle or with a recirculating loop accompanied by periodic feed topping. Selected runs were conducted in the feed and bleed mode. At the end of each experiment, the membranes were thoroughly flushed with condensed steam (pan condensate) diluted with raw water. The membrane fouling, expressed as a percentage drop in the water permeability, was estimated by measuring the pure water flux both before and after the cane juice UF. The membranes were then cleaned in place using

Table 1
Membrane module details

Membrane module[a]	Manufacturer	Membrane material	Module dimensions (cm×cm)[b]	Effective filtration area (m^2)	PWP[c] (LMH per kg/cm^2)
PPE0106 (40 mil)	Permionics, India	Polyether sulphone	6.35×102	2.2	58.0
PPE0106 (60 mil)	Permionics, India	Polyether sulphone	6.35×81	1.0	12.5[d]
PPE0106 (80 mil)	Permionics, India	Polyether sulphone	6.35×93	1.4	29.1, 33.87[e]
Cellpore® (0.8 mm)	Inchema, Switzerland	Modified polysulphone	8×47	1.3	

[a] Nominal molecular weight cutoff 20 kDa.
[b] Diameter×length.
[c] PWP experimental values, obtained at ambient temperature (~30°C) with new modules.
[d] Used module, cleaned before PWP measurement.
[e] Different batches of modules.

and use of the product. This information and labeling provides various forms of information utilized by health care professionals and patients that describes the composition, dosage, the use, and various other parameters of the medicament required by regulatory agencies, such as the United States Food and Drug Administration.

FIGS. **5** and **6** show an article of manufacture including packaging material **22**, a fluid dispensing apparatus or MDI **34** for dispensing metered amounts of fluid material **76** from a reservoir **64**. In one exemplary embodiment, the fluid dispensing apparatus **34** can include a container **34** defining a reservoir **64**, and a dispensing valve **60**. The dispensing valve **60** can include a metering chamber body **62**, defining a metering chamber **66** and having one or more metering chamber ports **68**; and a stem **42** allowing for slideable movement within the metering chamber body **62**. The stem **42** has a dispensing passage **70** and is connected to a sealing segment **72** allowing for slideable movement over the one or more metering chamber ports **68**. The present invention is not limited to the fluid dispensing apparatus shown in FIG. **5** and can include other types of fluid dispensing devices.

The stem **42** and sealing segment **72** can be moveable such that in a first position the metering chamber **66** is fluidically isolated from the dispensing passage **70**, and the metering chamber **66** is in fluidic communication with the reservoir **64** through the one or more metering chamber ports **68** and the dispensing passage **70**. In a second position (as shown in FIG. **5**), the metering chamber **66** is in fluidic communication with the dispensing passage **70**; and the metering chamber **66** is fluidically isolated from the reservoir **64** by the sealing segment **72** occluding the one or more metering chamber ports **68** and the stem occluding the dispensing passage **70**. Also shown in FIG. **5**, is fluid material **76** containing a safe and effective medicamem and a pharmaceutically acceptable carrier or diluent or propellant.

The dispensing valve **60** can further include an upper sealing sleeve **78** and lower sealing sleeves **80** and **80'**. Stem **42** is positioned for slideable movement within metering chamber **7** through the lower and upper aperture containing lower sealing sleeves **80** and **80'** and the upper sealing sleeve **78**.

Flange **82** and spring **84** define the limits of travel for stem **42**. Within these limits of travel, the stem **42** occupies an infinite number of positions which include the above mentioned first and second positions. In FIG. **5**, stem **42** is biased toward the upper sealing sleeve **78** in the second position by physical force exerted by a user.

In FIG. **6**, a box **74** encloses the container storage system **20**. On the exterior of the box **74**, a label **55** is disposed which provides information relating to the composition contained within the MDI. The label **55** may be located on any side of the box **74**, that is most beneficial to the user. Further, as mentioned above, a package insert **65** may be disposed within the box **74** and outside the container storage system **20**.

The present invention also provides a method of storing a [redacted] water [redacted] permeable to vaporized propellant.

The method includes the step of filling the container **34** with the liquid propellant at a predetermined pressure and wrapping the container **34** with the flexible package **22** to form an enclosed volume **40** in which the first container **40** is disposed therein.

[redacted] package [redacted] volume **40**, so that the [redacted] whereby shelf life and performance of the drug and the propellant are increased. The packaged product can be stored for prolonged periods of time such as 1 month or more, 3 months or more or 6 months or more at temperatures such as 25, 30 or 40° C. and at relative humidities of 60 or 75% while maintaining acceptable product properties.

The invention further includes method steps drawn to providing a material **50** for absorbing moisture in the enclosed volume **40** and disposed adjacent to the container **34**.

EXAMPLES AND COMPARATIVE TESTS/ ANALYSIS

In order to evaluate the effectiveness of the method and package for storing a pressurized canister of the present invention, shelf-life tests were carried out upon packages **22** which contained MDIs such as salmeterol/HFA-134a inhalers, Albuterol/HFA-134a, and Fluticasone Propionate/HFA-134a inhalers. A first shelf-life test of Albuterol/HFA-134a inhalers showed that by placing an MDI into the package **22** containing silica gel desiccant or an absorbing mechanism **50**, it was possible to substantially reduce the amount of moisture ingression (measured in Parts Per Million or PPM) into the inhaler after three months of storage at 40° C. and at 85% relative humidity. See Table 1.

TABLE 1

Sample	Initial	1 month @ 40° C./85% RH	3 months @ 40° C./85% RH
Control (non overwrapped inhaler)	35 ppm	330 ppm	446 ppm
Inhaler sealed in foil overwrap with 10 g silica gel desiccant	35 ppm	106 ppm	178 ppm
Inhaler stored in Zantac Efferdose tube	35 ppm	158 ppm	198 ppm

Also included in Table 1 is data for MDIs which are stored in the prior art type tube containers. The prior art type tubes included a ZANTAC™ EFFERIDOSE™ tube. This type of tube is a plastic tube which contains silica gel desiccant. The silica gel is disposed in a resealable lid that closes the tube. This tube construction is similar to that used for a Schering product, VANCERIL™ double strength.

A second test was performed and the results indicate that the reduction of moisture content within the package **22** can improve overall product performance of the liquid contained within the pressurized container **34**, where the liquid includes an asthma treating drug and a propellant. In the second test, the experiment was performed where aged non-overwrapped salmeterol/HFA-134a inhalers were compared to MDIs provided in the package **22**. The experiment included non-overwrapped inhalers which were stored for three months at either 30° C./60% relative humidity or 40° C./75% relative humidity. The non-overwrapped inhalers were then placed in a desiccator containing phosphorous pentoxide. The non-overwrapped inhalers were then tested for moisture content and fine particulate mass (FPM—the moisture sensitive product performance test over the period of inhaler storage). The results of this test are presented in Table 2.

TABLE 2

	30° C/60% RH		40° C/75%	
Time	Moisture content, PPM	FPM, Mcg	Moisture content, PPM	FPM, Mcg
Initial	92	10.3	92	10.3
1 month non overwrapped	Not tested	Not tested	413	8.2
3 month non overwrapped	463	7.9	816	6.2
2 weeks storage	233	8.9	298	7.4
6 weeks storage	151	9.6	236	8.0

The data in Table 2 shows that loss and product performance (loss in FPM, for salmeterol) is directly related to change in moisture content. The results indicated that product performance of MDIs is reversible, although not 100% reversible. Therefore, if moisture causes loss in product performance, it is possible to retrieve and improve the product performance by removing moisture from the MDI during storage. Such is the result with the package **22** of the present invention. Thus, the data shows how product performance is improved by controlling the moisture content within the MDI with the present invention.

A third comparative stability test at various elevated storage conditions was performed on a batch of Salmeterol/HFA134a inhalers that were overwrapped shortly after manufacture and compared against a control of new-overwrapped inhalers from the same batch. The FPM and moisture determinations are summarized in Table 3 and 4. Table 3 shows the FPM over six months for the control group non-overwrapped MDIs compared to overwrapped MDIs (contained within the package **22** of the present invention). Table 4 shows the inhaler moisture content in Parts Per Million (or PPM) over six months for the control group of non-overwrapped meter dose inhalers compared to MDIs provided in the package **22** of the present invention.

The data in Table 3 shows that the fine particulate mass (FPM), measured in micrograms (μg), of the MDIs provided in the package **22** of the present invention decreases at a substantially slower rate than that of the control group of non-overwrapped meter dose inhalers. The data in Table 4 shows that the moisture content in part per million (ppm) over six months for the MDI provided in the package **22** of the present invention is less than the moisture content present adjacent to or within the MDIs which are not provided with any overwrap.

TABLE 3

	Fine Particulate Mass (in μg)					
	40° C/75% RH		25° C/60% RH		25° C/75% RH	
Time point (months)	Control	wrapped	Control	Wrapped	Control	wrapped
0	9.4	9.4	9.4	9.4	9.4	9.4
1	7.5	8.6	9.4	8.6	8.4	8.7
3	6.6	7.4	8.3	8.5	8.0	8.3
6	6.2	7.7	7.5	7.8	7.2	7.8

TABLE 4

	Moisture Content, (in ppm)					
	40° C/75% RH		30° C/60% RH		25° C/75% RH	
Time point (months)	Control	wrapped	Control	Wrapped	Control	wrapped
0	80	81	81	81	81	81
1	360	83	198	72	212	93
3	540	29	305	45	454	64
6	526	93	446	76	465	87

A fourth comparative test was performed on a control group of non-overwrapped MDIs containing fluticasone propionate/HFA-134a compared to MDIs of the same drug and propellant provided in the package **22** of the present invention. The MDIs of the present invention were manufactured and provided in the package **22** of the present invention shortly after the time of manufacture and placed on stability at various elevated storage conditions along side the control group of unwrapped inhalers from the same batch.

Table 5 of the fourth test summarizes the variation in the content uniformity at the six-month time period in addition to the moisture of the control group and the MDIs provided in the package **22** of the present invention. Table 5 shows the variation in content uniformity in percentage of the relative standard deviation (RSD) based on the values for a dose ex actuator obtained from ten cans at the end of use (final nominal use). This variation test was obtained over six months for the control group of non-overwrapped MDIs compared with MDIs provided in the package **22** of the present invention.

Table 6 shows the inhaler moisture content in parts per million or PPM over six months for the control group of non-overwrapped MDIs of the fluticasone propionate/HFA-134a type compared to MDIs of the same drug and propellant provided in the package **22** of the present invention. Table 5 demonstrates that the MDIs provided in the package **22** of the present invention have a substantially smaller standard deviation in product performance so that the MDI will typically have a consistent increased performance relative to non-overwrapped MDIs.

Table 6 further shows that the initial moisture content in parts per million for the MDIs **36** provided in the package **22** of the present invention significantly and substantially decreases while the moisture content of the control group of non-overwrapped MDIs substantially increases from the initial measurement of the moisture content.

TABLE 5

Time point	40° C/75% RH		30° C/75% RH	
(months)	control	wrapped	control	Wrapped
0	6	6	6	6
3	14	5	11	5
4			12	5
6			12	9

*RSD (%) = percentage relative standard deviation based on the values for dose ex actuator obtained from 10 cans at the end of use (final nominal dose).

140

the appropriate cleaning solution before storing in 0.5–1% formalin till the subsequent run.

2.3. Juice analysis

The juice pH was measured using a calibrated pH meter with automatic temperature compensation (Control Dynamics, India). The juice color and clarity were estimated at 580 nm with a spectrophotometer (Systronics, India). The brix, representing the total dissolved solids, was measured using a standardized brix spindle (0–10 or 10–20 brix range, Reige, Germany). The 'pol' (a measure of the total polarizing substances, primarily sucrose), was estimated using a polarimeter (Schmitz and Heinsch, Germany). The purity rise and the rejection of various juice components was calculated as follows:

$$\text{Purity (\%)} = \left(\frac{\text{Pol per cent juice}}{\text{Brix}}\right) \times 100$$

$$\text{Purity rise} = (\text{Purity})_{\text{permeate}} - (\text{Purity})_{\text{feed}}$$

$$\text{Brix rejection (\%)} = \left(1 - \frac{(\text{Brix})_{\text{permeate}}}{(\text{Brix})_{\text{feed}}}\right) \times 100$$

$$\text{Non-sugars rejection (\%)} = \left(1 - \frac{(\text{Brix} - \text{Pol})_{\text{permeate}}}{(\text{Brix} - \text{Pol})_{\text{feed}}}\right) \times 100$$

$$\text{Sugar rejection (\%)} = \left(1 - \frac{(\text{Pol})_{\text{permeate}}}{(\text{Pol})_{\text{feed}}}\right) \times 100$$

The calcium oxide (CaO) content was estimated by titration. All analytical methods were as per the mill's practice and were in accordance with the norms prescribed by the Sugar Technologists Association of India [13].

3. Results

Two different juice streams viz. raw juice and clarified juice were evaluated on single spiral elements. The raw juice, tapped from the raw juice heaters at 70°C, is a turbid, dark greyish green solution at a pH between 5.7 and 5.9. It has a high suspended solids content of 15–25 g/l. In the conventional clarification process, the raw juice is limed, sulphited, boiled and subsequently allowed to settle in a clarifier. The overflow from the clarifier constitutes the clarified juice stream which is then taken to the evaporators for concentration. The clarified juice at 102°C is typically yellowish brown with a pH in the 6.95–7.05 range. Though this juice is normally free from visible suspended particles, it is generally hazy due to the presence of colloidal matter and fine bagasse particles (bagacillo).

3.1. Raw juice

The experiments were conducted on heated raw juice that was limed, flocculated and allowed to settle for 20–30 min to remove the suspended solids [14]. The clear juice obtained from this step was prefiltered through SS filters (60 mesh followed by 120 mesh) before subjecting it to UF. The experiments with the Permionics spiral modules were conducted after hydrophilizing the polyethersulphone membrane surface by the adsorption of polyvinyl alcohol (PVA). The procedure involved circulating a 0.1% PVA solution over the membrane surface for approximately 5 min. The module was then flushed with water to remove the excess, unadsorbed PVA before conducting the juice UF. The membrane surface modification was performed since previous field trials on a crossflow module consistently exhibited a higher flux with the PVA adsorbed membrane [15]. Further, the corresponding membrane fouling was also lower (60% drop in pure water permeability (PWP) with surface modification as compared to 73.4% drop with the unmodified membrane).

Fig. 2 shows the effect of varying transmembrane pressure on the raw juice flux through different spiral modules. The pressure drop was 1.6–2 kg/cm^2 for both the Permionics modules and 1.1–2 kg/cm^2 for the Cellpore module. The flux data reported for each pressure is averaged over the first 10 min of operation once the pressure was stable (typically within 1–2 min). The 40 mil spiral from Permionics exhibited the highest flux of about 58 LMH at 2 kg/cm^2. The flux was twice that obtained with the 80 mil Permionics modules (29.4 LMH). A Cellpore® 32 mil module, which was tested for comparison, exhibited a flux of 30.2 LMH. Further, with both Permionics 80 mil and Cellpore® 32 mil modules, the flux plateau was reached earlier at 1 kg/cm^2. It was also observed that in the mass transfer controlled region, the Permionics spirals displayed a marginal flux decline with increasing pressure beyond 3 kg/cm^2.

TABLE 6

Time point	40° C./75% RH		30° C./75% RH	
(months)	control	Wrapped	control	Wrapped
0	375	398	398	398
3	351	50	412	81
~			408	83
6			523	80

Table 7 shows the loss of HFA-134a (in grams) for wrapped Albuterol 134a MDI's stored for 24 months at 30° C./60% RH and 40° C./75% RH. The data in Table 7 is a mean of 5 determinations from 3 separate batches of MDI's.

TABLE 7

	40° C./75% RH	30° C./60% RH
Loss of HFA134a from the can (g)	0.4	0.7
HFA134a remaining in the pack (g)	0.3	0.2

The results of the above mentioned tests, outlined by Tables 1–4, prove that loss in fine particulate mass (FPM) of MDIs is directly related to moisture content adjacent or within an MDI. The results tabulated in Tables 5–7 prove that variation of the content uniformity at the end life of the wrapped MDIs of the present invention is substantially less than non-wrapped MDIs. Therefore, substantial increases in product performance of MDIs **36** are possible with the package **22** of the present invention which substantially reduces or eliminates the ingression of moisture or water vapor into the enclosed volume **40**. Table 7 shows proof of the operation of the virtual one way valve mechanism that permits egression of HFA-134a from package **22**.

The invention being thus described, it will be obvious that the same may be varied in many ways. Such variations are not to be regarded as a departure from the spirit and scope of the invention, and all such modifications as would be obvious to one skilled in the art are intended to be included within the scope of the following claims.

What is claimed is:

1. An apparatus comprising:

a container containing a pressurized drug formulation comprising a propellant and a drug dispersed and/or dissolved in said propellant; and

an overwrap constructed from a moisture impermeable, flexible material enclosing said container.

2. The apparatus of claim **1**, further comprising a desiccant in said container.

3. The apparatus of claim **1**, wherein the desiccant is selected from the group consisting of a zeolite, alumina, silica gel, and combinations thereof.

4. The apparatus of claim **1**, wherein the desiccant is placed loosely in the container or as part of an assembly attached to the container.

5. The apparatus of claim **1**, wherein the propellant is selected from the group consisting of 1,1,1,2-tetrafluoroethane, 1,1,1,2,3,3,3-heptafluoro-n-propane, and combinations thereof.

6. The apparatus of claim **5**, wherein the propellant is 1,1,1,2-tetrafluoroethane.

7. The apparatus of claim **6**, wherein the drug is albuterol sulfate.

8. The apparatus of claim **6**, wherein the drug is fluticasone propionate.

9. The apparatus of claim **6**, wherein the drug is salmeterol xinafoate.

10. The apparatus of claim **6**, wherein the drug is a combination of fluticasone propionate and salmeterol xinafoate.

11. The apparatus of claim **6**, wherein the drug is beclomethasone dipropionate.

12. An apparatus comprising:

an aerosol dispenser for dispensing metered amounts of fluid material from a reservoir, the dispenser comprising a container defining a reservoir, and a dispensing valve;

a drug formulation located within said aerosol dispenser comprising a pharmaceutically acceptable medicament and propellant; and

a flexible package overwrapping and sealing said aerosol dispenser,

wherein said flexible package is impermeable to water vapor and permeable to said propellant,

and wherein said flexible package substantially prevents ingression of water vapor and particulate matter into said enclosed volume and permits egression of said propellant.

13. The apparatus of claim **12**, further comprising a brochure disclosing product information.

14. The apparatus of claim **12**, further comprising a container for enclosing said flexible package.

15. The apparatus of claim **12**, further comprising a desiccant in said container.

16. The apparatus of claim **12**, wherein the desiccant is selected from the group consisting of a zeolite, alumina, silica gel, and combinations thereof.

17. The apparatus of claim **12**, wherein the desiccant is placed loosely in the container or as part of an assembly attached to the container.

18. The apparatus of claim **12**, wherein the propellant is selected from the group consisting of 1,1,1,2-tetrafluoroethane, 1,1,1,2,3,3,3-heptafluoro-n-propane, and combinations thereof.

19. The apparatus of claim **18**, wherein the propellant is 1,1,1,2-tetrafluoroethane.

20. The apparatus of claim **19**, wherein the drug is albuterol sulfate.

21. The apparatus of claim **19**, wherein the drug is fluticasone propionate.

22. The apparatus of claim **19**, wherein the drug is salmeterol xinafoate.

23. The apparatus of claim **19**, wherein the drug is a combination of fluticasone propionate and salmeterol xinafoate.

24. The apparatus of claim **19**, wherein the drug is beclomethasone dipropionate.

25. An apparatus comprising:

a means for containing a pressurized drug formulation comprising a propellant and a drug dispersed and/or dissolved in said propellant; and

a moisture impermeable, flexible overwrapping means for enclosing the containing means, said overwrapping means containing said containing means.

26. An apparatus comprising:

an aerosol dispensing means for dispensing metered amounts of fluid material from a reservoir;

a drug formulation within said aerosol dispenser comprising a pharmaceutically acceptable medicament and propellant; and

a flexible, moisture impermeable packaging means for enclosing said aerosol dispensing means and for permitting egression of said propellant, said packaging means enclosing said aerosol dispensing means.

* * * * *

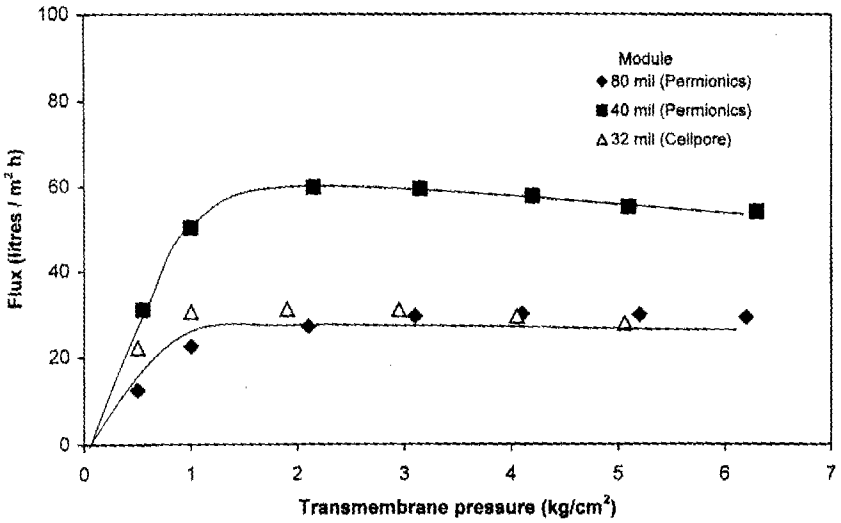


Fig. 2. Raw juice: effect of TMP (feed flow rate 24 l/min; pH 7.06–7.09; temperature 50–53°C).

The raw juice has a high suspended solids content mainly in the form of bagacillo. Earlier experiments have demonstrated that the fine particulate matter tends to deposit on the membrane surface during the course of raw juice UF [16]. The deposits form a secondary filtration layer that gets compressed at higher applied pressures. This increases the resistance to permeate flow and thus leads to flux decline with increasing pressure. Similar behavior has also been reported with 0.05 μm tubular ceramic membranes processing sugarcane juice at pressures of 2–23 kg/cm^2 and recirculation velocities of 1–5.5 m/s [7] as well as with other highly fouling liquid streams like acid whey and skim milk [16]. It was observed in our studies that the initial pre-treatment step involving flocculation aided in the formation of large flocs that could be eliminated by subsequent settling. However, complete removal of the bagacillo fines could not be effected even when the juice was filtered twice through 150 mesh SS sieves.

A comparison of the Permionics modules indicates that the flux improves with reduced channel size (Figs. 2 and 3). This is explained by the reasoning that a narrow channel results in a higher crossflow velocity (0.20 m/s for the 40 mil module as compared to 0.10 m/s for the 80 mil module). This, in turn, leads to better concentration polarization control in the 40 mil element. However, the behavior of the 32 mil Cellpore module was almost identical to that of the 80 mil Permionics module in spite of the difference in channel height. This could be caused by the higher fouling (69% reduction in water permeability) of the modified polysulphone membrane employed in the Cellpore module. On the contrary, the PVA adsorbed polyethersulphone membrane in the 80 mil Permionics spiral exhibited comparatively less fouling (45% drop in PWP).

The effect of channel height becomes particularly significant during long-term operation. Fig. 4 exhibits the UF of pre-treated raw juice on a Permionics 80 mil module. The experiment was conducted in a batch mode with retentate recycle accompanied by periodic feed topping. Once the feed volume was reduced by 20% (volume concentration factor 1.25X), the feed tank was replenished with fresh pre-treated raw juice equal to the volume of permeate withdrawn. Since cane juice is extremely prone to microbial degradation as well as sugar loss due to inversion with increased processing time, the feed was changed at regular intervals as marked in Fig. 4. After every 2–3 h of operation, the module was drained completely of the old feed and the experiment was continued with a fresh batch of feed, treated appropriately. No module cleaning was performed between feed changes.

~~142~~
142

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
DIRECCIÓN DE NUEVAS CREACIONES

2020
Bogotá, D.C.,

Doctor
EMILIO FERRERO
Abogado

ASUNTO	Radicación	04-44350
	Trámite	011
	Evento	378
	Actuación	430
	Oficio	3970
	Folios	04

Patente de Invención	X	Patente de Modelo de Utilidad			
Vía PCT (fase nacional)	X	Cap.I		Cap. II	x

No. Sol. Internacional PCT/GB02/05147
Fecha de Presentación Internal. 15 de noviembre de 2002

Como resultado del examen de fondo, realizado con fundamento en el artículo 45 de la Decisión 486 de la Comisión de la Comunidad Andina, se le comunica:

1. Documentos estudiados

Descripción:	Folios: 49 a 70	como se radico inicialmente
Reivindicaciones:	Folios: 129 a 134	modificadas
Dibujos:	Folios: 76 a 77	como se radicó inicialmente
Prioridad:	17 de noviembre de 2001, GB0127612.0	
	12 de noviembre de 2001, US60/340.705	

2. Objeto de la invención

Titulo de la invención:
Absorbentes y sus usos (folio 1).

El problema planteado en esta solicitud consiste en evitar la formación de aductos en envases para dispositivos médicos que comprende un medicamento.

Para solucionar este problema técnico se desarrolla un sistema compuesto por un envase impermeable, dispositivo medio y un material absórbete.

Clasificación internacional de Patentes (IPC) en B65D81/26

3. De la solicitud de Patente (según el caso)

Descripción (articulo 28 D 486)

- El solicitante debe presentar un nuevo titulo que permita identificar la materia

de la solicitud, ya que el actual no es preciso con el objeto de la solicitud de patente.

Reivindicaciones (artículo 30 D 486)

- Las frases "donde dicho medicamento es capaz de interactuar con las sustancia gaseosa para formar un aducto" en la reivindicación 1, "donde el material absorbente esta en una cantidad suficiente para prevenir la formación de un aducto" reivindicaciones 22 y 24 y "para prevenir al formación de un aducto" reivindicación 24, son un resultado a alcanzar, lo cual es inaceptable. Las reivindicaciones deben caracterizar un producto por la forma o constitución del mismo, las partes que lo componen y todo lo que permita establecer cómo se llego a tal resultado. No se aceptan reivindicaciones que caractericen resultados, usos, ventajas o efectos. Por lo anterior, debe eliminarse del capítulo en cuestión.
- La frase "y en donde la sustancia gaseosa es diferente al propulsor HFA (hidrofluoroalcano)" incluida como una característica técnica esencial de la reivindicación 1 y 24, no proporciona precisión ni concisión, ya que equivale a proteger todos los propulsores presentes y futuros disponibles en el estado de la técnica. Además dentro de la solicitud nunca se muestra una ventaja al no utilizar HFA.
  Así mismo, en la reivindicación 25 se dice "el medicamento es un antiinflamatorio usado en el tratamiento de enfermedades respiratorias", no proporcionando precisión ni concisión, ya que equivale a proteger todos los medicamentos antiinflamatorios, para el tratamiento de enfermedades respiratorias, presentes y futuros disponibles en el estado de la técnica.
- Los términos "sustancialmente" y "cantidad suficiente" utilizados en la reivindicación 24 y 35, deben eliminarse, ya que no proporcionan precisión ni concisión respecto a estas características técnicas.

Por lo anterior, el capítulo reivindicatorio no cumple con el requisito de claridad, de acuerdo al art. 30 de la Decisión 486.

4. Determinación del Estado de la Técnica

La fecha para determinar el estado de la técnica es el 14 de noviembre de 2003, de acuerdo al la fecha de prioridad invocada.
Tendiendo en cuenta la anterior fecha indicada, se realiza la búsqueda de las anterioridades de la presente solicitud, encontrándose los siguientes documentos relevantes:

N°	Documento	Título	Fecha de publicación
D1	US6179118	METHOD AND PACKAGE FOR STORING A PRESSURIZED CONTAINER CONTAINING A DRUG	2001-01-30

5. Análisis de patentabilidad (según requisito) (artículo 14 D486)

Es importante mencionar que el siguiente análisis de patentabilidad se realizó teniendo en cuenta las objeciones del numeral 3 de la presente comunicación.

Novedad (artículo 16 D486)

Respecto a la reivindicación 1:

La reivindicación 1 dice: "Un sistema que comprende:
a) Un dispositivo medico que comprende un medicamento y un componente que

gradualmente libera una sustancia gaseosa, en donde dicho medicamento es capaz de interactuar con la sustancia gaseoso par formar un aducto,

b) Una cantidad efectiva de un material adsorbente capaz de adsorber dicha sustancia gaseosa, y reduciendo o evitando de la formación de dicho aducto; y
c) Un paquete sellado que tiene un volumen incluido dentro del cual están situados el dispositivo y el material adsorbente, en donde el paquete sellado es sustancialmente impermeable a las sustancias gaseosas, y donde la sustancia gaseosa es diferente al propulsor HFA (hidrofluoroalcano)".

La reivindicación 24 dice: "un método para prevenir la formación de un aducto en un producto farmacéutico... que comprende las etapas:

I. Posicionar una cantidad efectiva de un material absorbente y el dispositivo médico dentro de un paquete sellable que es sustancialmente impermeable a las sustancias gaseosa;
II. Sellar el paquete para que el dispositivo medico y el adsorbente estén en un volumen envolvente dentro del paquete; y
III. Adsorber cualquier escape de las sustancia gaseosa del componente para prevenir la formación de una aducto".

Respecto al estado de la técnica:

D1 describe un producto farmacéutico que comprende un empaque sellado (22), una dispositivo medico (36) con un envase presurizado (34) que contiene un medicamento y un componente, y una cantidad efectiva de un absorbente (50). La válvula de medición (60) esta conformada por un polímero farmacológicamente inerte y resistente al propulsor, tal como el acetal (polioximetileno), poliamida, policarbonato, polifluorocarbono (Col 4 líneas 65-67). El medicamento puede ser triamcianolona acetonida (Col 5 línea 31) y como absorbente se utilizan tamices moleculares, silica gel, zeolitas, alúminas, bauxitas arcillas activadas (Col 8 líneas 11-28).

La invención también provee método para almacenar un envase que incrementa la vida útil del medicamento y el propulsor, que incluye los pasos:

- Proveer un empaque flexible (22) el cual es permeable al propulsor vaporizado e impermeable al vapor de agua,
- Proveer una material (50) para absorber la humedad en el volumen cerrado (40) y dispuesto adyacente al envase (34)
- Llenar el envase (34) con un propulsor líquido a determinada presión,
- Empacar el envase con un empaque flexible para formar una volumen envolvente (40).
- Sellar el empaque flexible, el cual encierra el volumen (40) previniendo el ingreso de vapor y cualquier material particulado en el volumen envolvente, mientras permite el egreso de vapores del propulsor (Col 13 líneas 56-67, Col 14 líneas 1-13).

Respecto a la solicitud en estudio:

Basado en la información de D1, donde la válvula de medida es de poliooximetileno, el cual esta disponible bajo la marca Derlin de Dupont siendo también conocida como poliacetal, y de acuerdo con lo divulgado por el solicitante este material libera una sustancia gaseosa (formaldehido). Es claro que la anterioridad D1 divulga todas las características técnicas del sistema conformado por el dispositivo médico, el material absorbente y el paquete sellado.

Dado lo anterior, el objeto de la invención recogido en las reivindicaciones 1 y 24 ha sido divulgado idénticamente en la anterioridad D1 por lo tanto estas

reivindicaciones y sus dependientes no se pueden considerarse nuevas.

6. Conclusión

Los requisitos de patentabilidad de la presente solicitud se encuentran afectados así:

N°	Documento N°	Reivindicación afectada	Requisito que afecta
D1	US6179118	1-35	Novedad

En cumplimiento del artículo 45 de la Decisión 486 de la Comisión de la Comunidad Andina, se le indica que debe dar respuesta dentro del término de 60 días contados a partir de la fecha de notificación de la presente comunicación. En caso de no dar respuesta al presente requerimiento, o si a pesar de la respuesta subsistieran los impedimentos para la concesión, se denegará la patente.

Notifíquese el presente oficio conforme a lo dispuesto en el numeral 5.2, literal e), del capítulo quinto del título primero de la Circular Única N° 10 de 2001.

ALIX CARMENZA CÉSPEDES DE VERGEL
Directora de División de Nuevas Creaciones (C)

El anterior requerimiento fue notificado por fijación en lista, de fecha 13 SET. 2010

CONCEPTO TÉCNICO N° 819	EXAMINADOR TÉCNICO Código N° 202090