122

Clarke, Modet & Cº

COLOMBIA

SEÑORES
SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
DIVISIÓN DE NUEVAS CREACIONES
E.S.D

REF EXPEDIENTE No.: 04 084.191
PATENTE : FORMULACION FARMACEUTICA EN AEROSOL QUE COMPRENDE FORMOTEROL O UN ESTEREOISOMERO
SOLICITANTE: CHIESI FARMACEUTICI S.p.A

ASUNTO: SOLICITUD ESTUDIO DE FONDO

DILIA RODRÍGUEZ D´ALEMAN, en mi condición de apoderada de la Sociedad solicitante, por el presente escrito atentamente solicito a Usted que habiéndose surtido la publicación de la presente solicitud, en la Gaceta de la Propiedad Industrial No.561 de fecha Febrero 28 , 2006 se proceda con el estudio de Fondo.

Para tal fin me permito anexar la tasa correspondiente No. 06.56-469.

Agradezco continuar con el presente trámite.

Señor Jefe,

DILIA RODRÍGUEZ D´ALEMAN
T.P.No. 20824 del CSJ

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SON: CIENTO NOVENTA Y CUATRO MIL PESOS

RESPONSABLE : _____

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Industria y Comercio
SUPERINTENDENCIA

DIVISIÓN DE NUEVAS CREACIONES

RADICACIÓN EXPEDIENTE No. 04-084191

EL EXTRACTO DE LA PRESENTE SOLICITUD DE **PATENTE DE INVENCIÓN**

FUE PUBLICADO EN LA GACETA DE PROPIEDAD INDUSTRIAL No **561** DE

FECHA **28** DE **FEBRERO DE 2006** EL TÉRMINO HÁBIL SEÑALADO POR LA

LEY EXPIRA EL **30** DE **MAYO** DEL **2006**

NOTA: Dentro del plazo de los seis (6) meses siguientes a partir de la fecha de publicación en la gaceta de Propiedad Industrial, deberá solicitar y cancelar el examen de patentabilidad so pena de que la solicitud caiga en abandono, de acuerdo con lo establecido en el Artículo 44 de la Decisión 486/2000.

SE PRESENTARON OPOSICIONES POR PARTE DE TERCEROS.

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(54) Stable pharmaceutical solution formulations for pressurised metered dose inhalers

(57) An aerosol solution composition for use in an aerosol inhaler comprises an active material, a propellant containing a hydrofluoroalkane, a cosolvent and optionally a low volatility component to increase the mass median aerodynamic diameter (MMAD) of the aerosol particles on actuation of the inhaler.
The composition is stabilized by using a small amount of mineral acid and a suitable can having part or all of its internal metallic surfaces made of stainless steel, anodized aluminium or lined with an inert organic coating.

EP 1 157 689 A1

Description

[0001] The invention relates to stable pharmaceutical solution to be used with pressurised metered dose inhalers (MDIs) suitable for aerosol administration. In particular, the invention relates to solution to be used with pressurised metered dose inhalers (MDIs), suitable for aerosol administration containing β_2-agonists and stable at room temperature for a pharmaceutically acceptable shelf-life.

[0002] Pressurised metered dose inhalers are well known devices for administering pharmaceutical products to the respiratory tract by inhalation.

[0003] Drugs commonly delivered by inhalation include bronchodilators such as β_2-agonists and anticholinergics, corticosteroids, anti-leukotrienes, anti-allergics and other materials that may be efficiently administered by inhalation, thus increasing the therapeutic index and reducing side effects of the active material.

[0004] MDI uses a propellant to expel droplets containing the pharmaceutical product to the respiratory tract as an aerosol. Formulations for aerosol administration *via* MDIs can be solutions or suspensions. Solution formulations offer the advantage of being homogeneous with the active ingredient and excipients completely dissolved in the propellant vehicle or its mixture with suitable co-solvents such as ethanol. Solution formulations also obviate physical stability problems associated with suspension formulations so assuring more consistent uniform dosage administration.

[0005] For many years the preferred propellants used in aerosols for pharmaceutical use have been a group of chlorofluorocarbons which are commonly called Freons or CFCs, such as CCl_3F (Freon 11 or CFC-11), CCl_2F_2 (Freon 12 or CFC-12), and $CClF_2$-$CClF_2$ (Freon 114 or CFC-114).

[0006] Recently, the chlorofluorocarbon (CFC) propellants such as Freon 11 and Freon 12 have been implicated in the destruction of the ozone layer and their production is being phased out.

[0007] Hydrofluoroalkanes [(HFAs) known also as hydro-fluoro-carbons (HFCs)] contain no chlorine and are considered less destructive to ozone and these are proposed as substitutes for CFCs.

[0008] HFAs and in particular 1,1,1,2-tetrafluoroethane (HFA 134a) and 1,1,1,2,3,3,3-heptafluoropropane (HFA 227) have been acknowledged to be the best candidates for non-CFC propellants and a number of medicinal aerosol formulations using such HFA propellant systems have been disclosed.

[0009] Due to the higher polarity of the HFA propellants, in particular of HF A 134a (dielectric constant D ≥ 9.5), with respect to CFC vehicles (D ≤2.3), HFA solution formulations may suffer to a greater extent of chemical stability problems with respect to the corresponding CFC formulations.

[0010] Preparation of stable HFA solution formulations is even more critical when bronchodilator β_2-agonists belonging to the class of the phenylalkylamino derivatives are concerned; said drugs, like formoterol (8-hydroxy-5-[(1R)-1-hydroxy-2-[[(1R)-2-(4-methoxyphenyl)-1-methylethyl]-amino]-ethyl]-2(1H)-quinolinone (hereinafter referred as TA 2005), and salbutamol (albuterol) and others, may suffer of inherent chemical stability problems due to their susceptibility to oxidative conditions; moreover, in the view of the presence of some functional groups like formamide, a higher polarity of the vehicle may accelerate the rate of solvolysis reactions.

[0011] As far as formoterol, the currently marketed CFC solutionformulation (Foradil®) exhibits a limited shelf life, i. e. 12 months at refrigerator temperature, 4± 2°C, and only 3 month at room temperature.

[0012] As far as salbutamol, no formulation as HFA solution for aerosol administration currently on the market.

[0013] In the case of TA 2005, no formulation at all is currently available for aerosol administration.

[0014] In consideration of the problems outlined, it would be highly advantageous to provide a formulation in the form of HFA solution to be administered by MDI's aimed at providing pharmaceutical doses of β_2-agonists characterised by adequate shelf-life.

OBJECT OF THE INVENTION

[0015] It is an object of the invention to provide a formulation in the form of HFA solution to be administered by MDI's for providing pharmaceutical doses of β_2-agonists into the low respiratory tract of patients suffering of pulmonary diseases such as asthma, characterised by adequate shelf-life. In particular, it is an object of the invention to provide a formulation in the form of HFA solution to be administered by MDI's for providing pharmaceutical doses of formoterol with a greater shelf-life of that of the formulation currently on the market.

[0016] According to the invention there is provided a pharmaceutical composition comprising a β_2-agonist belonging to the class of phenylalkylamino derivatives in a solution of a liquefied HFA propellant, a co-solvent selected from pharmaceutically acceptable alcohols, solution whose apparent pH has been adjusted to between 2.5 and 5.0 by addition of small amounts of a mineral acid. The composition of the invention shall be contained in a pressurised MDI having part or all of its internal metallic surfaces made of stainless steel, anodised aluminium or lined with an inert organic coating.

[0017] In fact, it has been found that, in the case of certain active ingredients such as β_2-agonists, their chemical stability in HFA solution formulations could be dramatically improved by a proper and combined selection of the kind

of cans as well as the apparent pH range. The attribution 'apparent' is used as pH is indeed characteristic of aqueous liquids where water is the dominant component (Mole Fraction > 0.95). In relatively aprotic solvents such as the HFA-ethanol vehicles used in these studies, protons are non-hydrated; their activity coefficients differ significantly from those in aqueous solution. Although the Nernst equation with respect to EMF applies and the pH-meter glass electrode system will generate a variable milli-volt output according to proton concentration and vehicle polarity, the "pH" meter reading is not a true pH value. The meter reading represents an apparent pH or acidity function (pH').

[0018] When formoterol fumarate was titrated with a strong acid in a model vehicle system commercially available (HFA 43-10MEE, Vertrel XF, Dupont), according to a method developed by the applicant, the pH' profile exhibits a shallow negative to about pH' = 5.5; thereafter the acidity function drops abruptly. Surprisingly the corresponding HFA formulations turned out to much more stable below pH' 5.5. As far as TA 2005 is concerned, the pH' profile exhibits a shallow negative to about pH' = 5.0; thereafter the acidity function drops quite abruptly.

[0019] On the other hand, the use of inert containers allows to avoid the leaching of metal ions or alkali as a consequence of the action of the acid contained in the formulation onto the inner walls of the cans. Metal ions such Al^{3+} or alkali respectively deriving from the conventional aluminium or glass cans could in turn catalyse radical oxidative or other chemical reactions of the active ingredient which give rise to the formation of degradation products.

[0020] According to an embodiment of the invention there is also provided a pharmaceutical composition further containing a low volatility component in such a way as to, besides increasing the mass median aerodynamic diameter (MMAD) of the aerosol particles on actuation of the inhaler as explained in the following, further improving the stability of the formulation. In fact, the addition of a low volatility component with a reduced polarity with respect to the co-solvent such as an ester may allow either to reduce the amount of acid to be added for adjusting the pH and diminish the polarity of the medium so limiting the possible uptake of environmental water. In the case of active ingredients such as formoterol, it is well known that the latter (e.g. humidity) could be detrimental to the stability of the active ingredient during storage. According to a particular embodiment of the invention, there is provided a pressurised MDI for administering pharmaceutical doses consisting of an anodised aluminium container filled with a pharmaceutical composition consisting of a solution of formoterol fumarate in HFA 134a as a propellant in turn containing 12% *w/w* ethanol as a co-solvent and optionally isopropyl myristate as a low volatility component in an amount less/equal than 1.0% w/w, the apparent pH of said solution having been adjusted to between 3.0 and 3.5 by addition of small amounts of hydrochloric acid. The expression '% w/w' means the weight percentage of the component in respect to the total weight of the composition.

[0021] The shelf-life of the formulation put in the device of the invention could be predicted to be greater than two years at the refrigerator temperature (4-10° C) and three months at room temperature.

[0022] According to another particular embodiment of the invention, there is provided a pressurised MDI consisting of a coated container filled with a pharmaceutical composition consisting of a solution of a combination of formoterol fumarate and beclometasone dipropionate (hereinafter BDP) in HFA 134a as a propellant in turn containing 12% *w/w* ethanol as a co-solvent with or without isopropyl myristate as low volatility component, the apparent pH of said solution having been adjusted to between 3.0 and 3.5 by addition of small amounts of hydrochloric acid.

[0023] According to a further particular embodiment of the invention, there is provided a pressurised MDI consisting of a coated container filled with a pharmaceutical composition consisting of a solution of TA 2005 in HFA 134a as a propellant in turn containing 12% *w/w* ethanol as a co-solvent with or without ispropyl myristate as a low volatility component, the apparent pH of said solution having been adjusted to between 3.0 and 5.0 by addition of small amounts of hydrochloric acid.

[0024] However, a person sufficiently skilled in the art can easily apply the teaching of the present invention to the preparation of HFA solution formulations containing other active ingredients bearing functional groupssensitive to hydrolytic and/or oxidative reactions, such as formamide and cathecol respectively.

[0025] WO 97/47286, EP 513127, EP 504112, WO 93/11747, WO 94/21228, WO 94/21229, WO 96/18384, WO 96/19198, WO 96/19968, WO 98/05302, WO 98/34595 and WO 00/07567 disclose HFA formulations in the form of suspensions in which β_2-agonists such formoterol and salbutamol are either exemplified and/or claimed.

[0026] WO 99/65464 refers to HFA formulations containg two or more active ingredients in which at least one is in suspension. The preferred formulations comprises salbutamol sulphate in suspension.

[0027] In WO 98/34596, the applicant described solution compositions for use in an aerosol inhaler, comprising an active material, a propellant containing a hydrofluoroalkane (HFA), a cosolvent and further comprising a low volatility component to increase the mass median aerodynamic diameter (MMAD) of the aerosol particles on actuation of the inhaler. Said application does not address the technical problem of the chemical stability of the active ingredient but it rather concern the drug delivery to lungs.

[0028] In the international application n°PCT/EP99/09002 filed on 23/11/99 published on June 2, 2000 as WO 00/30608 the applicant has disclosed pressurised MDI's for dispensing solution of an active ingredient in a hydrofluorocarbon propellant, a co-solvent and optionally a low-volatility component characterized in that part or all of the internal surfaces of said inhalers consist of stainless steel, anodised aluminium or are lined with an inert organic coating. The

examples are referred only to steroids and anticholinergic agents. As demonstrated in the example 1 of the present application, the use of coated containers, even in the presence of an organic acid, is not sufficient for providing stable solution formulations of a phenylalkylamino derivative such as salbutamol.

[0029] EP 673240 proposes the use of acids as stabilisers preventing the chemical degradation of the active ingredient in aerosol solution formulations comprising HFAs. Most examples relate to ipratropium bromide, an anticholinergic drug and only an example is presented for a β_2-agonist, i.e. fenoterol. Although salbutamol is claimed, no exemplary formulations are provided. Moreover, the stability data are reported only for ipratropium and the patentee does not either make difference between the use of organic and inorganic acids. It is indeed evident from the data reported in the example 1 of the present application, that salbutamol cannot be stabilised at all by addition of organic acids even when stored in coated cans. Furthermore, apart from ipratropium bromide, in EP 673240 no guidance is given with respect to the amount of acid which has to be added in order to stabilise the medicaments without compromising the stability of the whole composition in the can. The only hint can be found on page 5, lines 15 to 16 which says that an amount of inorganic acid should be added to obtain a pH value from 1 to 7, so a very broad and generic range.

[0030] WO 98/34596 refers to solution formulations containing a propellant and a physiologically acceptable polymer which could help the solubilisation and the stability as well of the active ingredients.

[0031] WO 00/06121 refers to propellant mixtures for aerosol dinitrogen monoxide and a hydrofluoroalkane in the preparation of suspension and solution aerosols. The use of dinitrogen monoxide may improve the stability at storage of oxidation-sensitive active ingredients. As far as β_2-agonist such as levosalbutamol sulphate, formoterol fumarate and salmeterol xinafoate, only examples referred to suspensions are reported.

[0032] WO 99/65460 claims pressurised MDI's containing stable formulations of a β-agonist drug in suspension or solution. Examples refer to solutions of formoterol fumarate containing an HFA propellant and ethanol as co-solvent, filled in conventional aluminium or plastic coated glass cans.

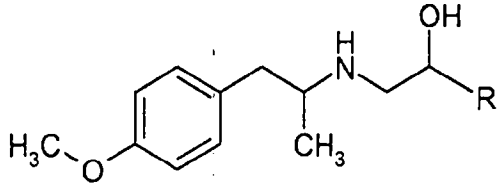
[0033] Samples stored under accelerated conditions (40° C, 75% relative humidity) for a very short period, one month, exhibited about 10% loss of drug. According to pharmaceutical guidelines on stability, loss of 10% of active ingredient does not meet the criteria of acceptance. Moreover, as it is evident from the data reported in Example 2 of the present application, following the teaching of WO 99/65460 stable formoterol solution formulations cannot be provided. The applicant has indeed demonstrated that the presence of low-volatility components does not substantially affect the chemical stability of the compositions. In some cases, they could even improve it.

[0034] According to a further aspect of the invention there is provided a method of filling an aerosol inhaler with a composition of the invention, the method comprising:

(a) Preparation of a solution of one or more active ingredients in one or more co-solvents optionally containing an appropriate amount of a low volatility component
(b) Filling of the device with said solution
(c) Adding a pre-determined amount of a strong mineral acid
(d) Adding a propellant containing a hydrofluoroalkane (HFA)
(e) Crimping with valves and gassing

[0035] Active ingredients which may be used in the aerosol compositions of the invention are short- and long-acting β_2-adrenergic agonists such as salbutamol, formoterol, salmeterol, TA 2005 and salt thereof and their combinations with steroids such as beclomethasone dipropionate, fluticasone propionate, budesonide and its 22R-epimer or with anticholinergic-atropine-like derivatives such as ipratropium bromide, oxitropium bromide, tiotropium bromide.

[0036] Preferably the active ingredient is a long acting β_2-agonists belonging to the formula sketched below



wherein R is more preferably 1-formylamino-2-hydroxy- phen-5-yl (formoterol) or 8-hydroxy-2(1H)-quinolinon-5-yl (TA 2005) or one of their corresponding stereoisomers. Other amino type drugs bearing functional groups sensitive to oxidative and/or hydrolytic reactions can be advantageously used. Although the preferred formulations of the invention are in the form of solutions, in case of the combinations, one of the two active ingredients could be present in suspension.

[0037] We prefer the formulation to be suitable for delivering a therapeutic amount of the active ingredient in one or two actuations. Preferably the formulation will be suitable for delivering 6-12 µg/dose of formoterol fumarate either alone or in combination. In the case of TA 2005, the formulation will be advantageously suitable for delivering 2-10 µg/dose, preferably 3-5 µg/dose. For "dose" we mean the amount of active ingredient delivered by a single actuation of the inhaler.

[0038] The formulations of the invention will be contained in cans having part of all of the internal surfaces made of anodised aluminium, stainless steel or lined with an inert organic coating. Examples of preferred coatings are epoxy-phenol resins, perfluoroalkoxyalkane, perfluoroalkoxyalkylene, perfluoroalkylenes such as polytetrafluoroethylene, fluorinated-ethylene-propylene, polyether sulfone and a copolymer fluorinated-ethylene-propylene polyether sulfone. Other suitable coatings could be polyamide, polyimide, polyamideimide, polyphenylene sulfide or their combinations.

[0039] To further improve the stability, cans having a rolled-in rim and preferably a part or full rollover rim are used.

[0040] The formulation is actuated by a metering valve capable of delivering a volume of between 50 µl and 100 µl.

[0041] Metering valves fitted with gaskets made of chloroprene-based rubbers can preferably be used to reduce the ingress of moisture which, as previously mentioned, can adversely affect the stability of the drug during storage. Optionally, further protection can be achieved by packaging the product in a sealed aluminium pouch.

[0042] The hydrofluorocarbon propellant is preferably selected from the group of HFA 134a, HFA 227 and mixtures thereof.

[0043] The co-solvent is usually an alcohol, preferably ethanol.

[0044] The low volatility component, when present, has a vapour pressure at 25°C lower than 0.1 kPa, preferably lower than 0.05 kPa. Advantageously, it could be selected from the group of glycols, particularly propylene glycol, polyethylene glycol and glycerol or esters, for example ascorbyl palmitate, isopropyl myristate and tocopherol esters.

[0045] The compositions of the invention may contain from 0.1 to 10% w/w of said low volatility component, preferably between 0.3 to 5% w/w, more preferably between 0.4 and 2.0% w/w.

[0046] Propylene glycol, polyethylene glycol, glycerol with residual water less than 0.1% w/w and esters of long-chain fatty acids are the preferred low-volatility components. More preferred are those with a dipole moment less than 2.0 or with a dielectric static constant less than 20, preferably less than 10. Particularly preferred is isopropyl myristate.

[0047] The function of the low volatility component is to modulate the MMAD of the aerosol particles and optionally to further improve the stability of the formulation. With respect to the latter aspect, particularly preferred is the use of isopropyl myristate.

[0048] The apparent pH range is advantageously comprised between 2.5 and 5.0, preferably between 3.0 and 4.5, even more preferably between 3.0 and 3.5. Strong mineral acids such as hydrochloric, nitric, phosphoric are preferably used to adjust the apparent pH.

[0049] The amount of acid to be added to reach the desired apparent pH will be pre-determined in the model vehicle reported before and it will depend on the type and concentration of the active ingredient. In the case of the preferred formulations of formoterol fumarate and its combination with beclometasone dipropionate, an amount comprised between 3 and 3.5 µl of 1.0 M hydrochloric acid should be added.

[0050] The following examples further illustrate the invention.

Example 1

Stability of salbutamol (100 µg/dose)-HFA 134a solution as such and in the presence of different organic acids.

[0051] Compositions containing 24 mg of salbutamol (100 µg/dose), 10-20% (w/w) ethanol in HFA 134a put in 12 mL epoxy phenol resin lacquered cans, with or without addition of different organic acids, were stored at 40- 50° C.

[0052] The results in term of stability expressed as percentage of remaining drug determined by HPLC, are reported in Table 1.

Table 1

% SALBUTAMOL		
Acid	**t = 42 days**	**t= 1.5 months at 4° C**
None	69%	-
Oleic	69-70%	-
Xinafoic	70%	-
Citric (0.41 w/w)	-	40.0
Citric (0.02 w/w)	-	55,1
30% Acetic acid (0.4% w/w)	-	49.6

Table 1 (continued)

% SALBUTAMOL		
Acid	**t = 42 days**	**t= 1.5 months at 4° C**
30% Acetic acid (0.14% w/w)	-	73.8

[0053] The results show that the addition of organic acids does not improve the stability of salbutamol even when coated cans are used.

Example 21

Stability of formoterol (12μg/100μl) -HFA 134a compositions in epoxy-phenol resin lacquered cans.

[0054] Solution formulations were prepared by dissolving 1.44 mg of formoterol fumarate in HFA 134a in turn containing 15% w/w ethanol and 1.3% w/w glycerol. pMDIs were stored upright over the range 4-50°C for up to 28 days. Formoterol content was determined by HPLC and the percent residual concentrations calculated relative to the 12μg/shot nominal dose. The percent residual formoterol concentration is reported in Table 2. Derived Arrhenius parameters were used to estimate rate constants at ambient temperature (18-25°) and solutions stored in a domestic refrigerator (4-10°); these rate constants were used to calculate predicted shelf-life for 5% and 10% degradation of formoterol (Table 3).

[0055] The calculated shelf-life data in Table 3 indicates that formoterol is not stable in this HFA 134a-ethanol-glycerol vehicle.

Table 2:

Degradation Rate Data for Formoterol-HFA 134a pMDI Solutions (12μg/100μl) Vehicle: HFA 134a with 1.3% w/w Glycerol, 15.0% w/w Ethanol Epoxy-phenol lacquered cans stored upright					
Time (days)	Percent Residual Conc. Formoterol				
	50°C	43°C	40°C	25°C	4°C
Initial	99.7	99.7	99.7	99.7	99.7
2	92.5	-	-	-	-
4	87.2	89.4	-	-	-
6	80.6	-	-	-	-
7	-	-	89.0	-	-
10	74.9	-	-	-	-
12	72.1	79.4	-	-	-
14	67.0	-	81.7	92.0	-
16	64.4	75.7	-	-	-
18	59.5	-	-	-	-
20	59.5	74.5	-	-	-
24	54.6	68.6	-	-	-
28	47.2	63.3	71.3	86.6	96.7
r	0.995	0.989	0.993	0.997	-
Rate Constant ($day^{-1} \times 10^2$)	2.53	1.49	1.17	0.51	0.11
Arrhenius Plot Parameters: $K = Ae^{E/RT}$ $A = 2.28 \times 10^6\ day^{-1}$: $E = 49.4\ kJ\ mol^{-1}$; $r = 0.9985$					

Table 3:

Predicted Shelf Life Data for Formoterol-HFA 134a pMDI Solutions (12µg/100µl) Vehicle: HFA 134a with 1.3% w/w Glycerol, 15% w/w Ethanol Epoxy-phenol lacquered cans stored upright			
Temperature	**Rate Constant (day^{-1} x 10^3)**	**Shelf-Life (days)**	
		$t_{10\%}$	$t_{5\%}$
4°C	1.10	95	47
10°C	1.74	60	29
20°C	3.51	30	15
25°C	4.93	21	10

Example 3

Effect of hydrochloric acid on solution pH' (acidity function)

[0056]

(a) 1.0 M hydrochloric acid was added incrementally to 50 mL of HFA 43-10MEE (Vertrel XF) containing 20% w/w ethanol and pH' measured after each aliquot of acid. Figure 1 shows the resultant titration curve normalised to the usual fill volume of a pMDI can (12 L). The pH' profile exhibits a shallow negative slope to about pH'=5.5; thereafter the acidity function drops abruptly.

(b) Experiment (a) was repeated with formoterol formulations containing a lower concentration of ethanol (12% w/w) and with the addition of 1.0% isopropyl myristate. The resultant pH profile, for replicate bulk solutions, shown in Figure 2 is similar in shape with the abrupt fall in pH' per unit increment of acid again commencing at about pH' = 5.5. However, only about half the acid is required to achieve the same reduction in pH'. This is largely due to the reduction in ethanol content; Figure 2 also shows similarity in the profiles obtained with and without isopropyl myristate.

Example 4

Effect of pH' on Stability of Formoterol Solutions in HFA 43-10MEE containing 20% w/w ethanol

[0057] Aliquots of 1.0 M hydrochloric acid were added to 12 mL of formoterol solution in glass vials. After measurement of pH, valves were crimped on and the vials stored upright at 50°C. Vial samples containing different concentrations of acid were assayed for residual formoterol after 10 and 20 days storage. The pH' of a third vial was determined after 40 days storage. Results are shown in Table 4. Table 4 shows changes in pH on storage; this is probably largely associated with leaching of alkali from the soft glass of the vials. However, overall consideration of the pH' and formoterol content data implies that the stability of a solution formulation of the drug in HFA can be improved by the addition of mineral acid to provide a formulation with pH' between 2.5-5.0.

Table 4:

pH' and Formoterol Content of Formoterol-Vertrel XF/HFA Solutions (12µg/100µl) Vehicle: Vertrel XF/HFA with 20% Ethanol and Hydrochloric Acid St Gobain glass vials stored upright				
Acidity Function (pH')		**Percent Residual Conc. Formoterol**		
Initial	**40 days**	**Initial**	**10 days**	**20 days**
1.8	2.8	100	4.8	Nil
2.1	4.4	100	75.1	70.7
2.6	4.2	100	97.2	86.7
3.3	4.2	100	97.1	89.9

Table 4: (continued)

pH' and Formoterol Content of Formoterol-Vertrel XF/HFA Solutions (12µg/100µl) Vehicle: Vertrel XF/HFA with 20% Ethanol and Hydrochloric Acid St Gobain glass vials stored upright				
Acidity Function (pH')		**Percent Residual Conc. Formoterol**		
Initial	**40 days**	**Initial**	**10 days**	**20 days**
5.6	6.6	100	95.8	92.1
7.4	6.7	100	85.4	67.2

Example 5

Stability of acidified formoterol-HFA 134a solutions in anodised cans

[0058] Formoterol formulations (12µg/100µl) were prepared by dissolving 1.44 mg of formoterol fumarate in HFA 134a containing 12% *w/w* ethanol with and without 1.0% *w/w* isopropyl myristate. The latter was included as a non-volatile excipient with the potential for increasing MMAD if so desired. It also improves the solubility of formoterol in the vehicle and reduces polarity of the vehicle compared to the addition of glycerol.

[0059] pMDI cans containing 3.1-3.4µl 1.0 M hydrochloric acid were set down on storage, upright and inverted, at 4°C to 50°C and samples taken for analysis of formoterol content at appropriate intervals.

[0060] Stability data obtained after 70 days of storage are given in Table 5.

[0061] A matrix of formulations containing 1.44 mg (12µg/100µl) formoterol fumarate were prepared in HFA 134a containing 12.0% *w/w* ethanol with or without 1.0% *w/w* isopropyl myristate as non-volatile excipient. Aliquots of drug concentrate were transferred to anodised cans and 3.15-3.35 µl of 1.0M hydrochloric acid added prior to crimping with 50µl valves and gassing between 22 and 28 replicates at each acid strength were prepared.

[0062] To determine residual formoterol, 30 x 50µl shots were discharges into DUSA tubes. The acid range selected was anticipated to give pH' values of 3.0-3.5 and to determine the formulation sensitivity to small changes in acid concentration. Cans were placed on stored upright and inverted (valve up and down respectively) at 25-50°C.

[0063] Table 5 shows the results obtained at 40° and 50° after 11-40 day's storage. Each value (expressed as per cent nominal drug concentration) is obtained from a different can.

[0064] Initial values were obtained for two cans of each acid strength. Inspection of the data shows all assay values to within the reproducibility of the HPLC assay and independent of acid strength. A similar conclusion was drawn for the storage time point replicates, i.e., independent of acid strength (3.2-3.3µl) or whether cans were stored upright or inverted. Consequently for kinetics calculation the mean value for initial (n=10) and subsequent time points (n=6) was used.

[0065] In Table 6 are reported the Arrhenius parameters together with estimated shelf lives at 4, 10 and 25°C. The $t_{5\%}$ is predicted to be greater than 3 months at ambient temperature and approximately 2 years at 4°C.

Example 6

Stability of acidified formoterol/BDP-HFA 134a solutions in cans coated with a fluorocarbon polymer (DuPont 3200-200).

[0066] Formoterol and BDP combination formulations equivalent to doses of 6 µg/50 µl and 100 µg/50 µl respectively, were prepared by dissolving 1.44 mg of formoterol fumarate and 24 mg of BDP in HFA 134a containing 12% *w/w* ethanol and 0.4% w/w of isopropyl myristate. pMDI coated cans containing 3.25 µl 1.0 M hydrochloric acid were set down on storage inverted, at 4°C and samples taken for analysis of formoterol and BDP contents at appropriate intervals.

[0067] Stability data obtained are given in Table 7.

[0068] Each value is expressed as per cent nominal drug concentration.

[0069] The results indicate that the formulation is stable for at least 4 months at 4° C.

Example 7

Stability of acidified TA 2005-HFA 134a solutions in cans coated with a fluorocarbon polymer (DuPont 3200-200).

[0070] TA 2005 (3.5 µg/50 µl) were prepared by dissolving 0.84 mg of the active ingredient in HFA 134a containing 12% *w/w* ethanol and 1.0% w/w of ispropyl myristate. pMDI coated cans containing 1.0 , 1.4 and 1.8 µl 0.08 M hydrochloric acid (corresponding respectively to an apparent pH of about 4.8, 3.2 and 2.9) were set down on storage, upright at 50°C, and samples taken for analysis of TA 2005 contents at appropriate intervals.

[0071] Stability data obtained are given in Table 8.

[0072] Each value is expressed as per cent nominal drug concentration.

[0073] The results indicate that the formulations in which the apparent pH is comprised between 3.0 and 5.0 are stable (i.e give rise to much less than 10% loss of drug) for almost three months at 50° C, while that corresponding to an apparent pH of less than 3, not.

Table 7:

Formoterol/BDP combination formulations of Ex 6 - Stability data at 4°C			
	Storage Condition		
	Initial	4°C; 64 days inverted	4°C; 123 days inverted
Formoterol	104.7	95.10	99.9
BDP	99.4	100.10	102.6

Table 8:

TA 2005 formulations of Ex 7 - Stability data at 50°C			
	Storage Condition		
0.08M HCl µl per can	Initial	50°C; 22 days upright	50°C; 83 days upright
1.0	100.0	98.3	99.4
1.4	100.0	98.2	98.8
1.8	100.0	90.2	88.1

Claims

1. An aerosol composition which comprises a β_2-agonist drug of the phenylalkylamino class bearing a functional group sensitive to oxidative and/or hydrolytic reaction in a solution of a liquefied HFA propellant, a co-solvent selected from pharmaceutically acceptable alcohols, wherein the pH of the solution -is comprised between 2.5 and 5.0 by addition of small amounts of a mineral acid such as hydrochloric, nitric or phosphoric acid.

2. A composition according to claim 1 wherein the active ingredient is a β_2-agonist selected from salbutamol, formoterol, salmeterol and TA-2005, salts thereof or their combination with steroid such as beclomethasone dipropionate, fluticasone propionate, budesonide and its 22R-epimer or an anticholinergic atropine-like derivative such as ipratropium bromide, oxitropium bromide, tiotropium bromide

3. A composition according to claims 1-2 filled in a container having part or all of its internal metallic surfaces made of stainless steel, anodised aluminium or lined with an inert organic coating.

4. A composition according to claims 1-3, wherein the container is lined with an inert organic coating selected from epoxy-phenol resins, perfluoroalkoxyalkane, perfluoroalkoxyalkylene, perfluoroalkylenes such as polytetrafluoroethylene, fluorinated-ethylene-propylene, polyether sulfone and a copolymer fluorinated-ethylene-propylene polyether sulfone

5. A composition according to claims 1-4, wherein the active ingredient is formoterol fumarate and the pH of the solution -is comprised between 3.0 and 3.5.

6. A composition according to claims 1-5, wherein the solution includes a low volatility component with a vapour pressure at 25°C not more than 0.1 kPa, preferably not more than 0.05 kPa.

7. A composition according to any preceding claim, wherein the solution includes at least 0.2% by weight of the low volatility component and not more than 10% by weight.

8. A composition according to claims 6-7, wherein the low volatility component is selected from a glycol or an ester of long-chain fatty acids.

9. A composition according to claims -6-8, wherein the low volatility component is isopropyl myristate.

10. A composition according to any preceding claim, wherein the propellant includes one or more HFAs selected from the group comprising HFA 134a and HFA 227.

11. A composition according to any preceding claims , wherein the cosolvent is an alcohol, preferably ethanol.

12. A method of preparing the formulations of claims 1-10 , the method comprising:

(a) preparation of a solution of one or more active ingredients in one or more co-solvents optionally containing an appropriate amount of a low volatility component;
(b) filling the device with said solution ;
(c) adding a pre-determined amount of a strong mineral acid ;
(d) adding a propellant containing a hydrofluoroalkane (HFA);
(e) crimping with valves and gassing.

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(54) Title: PRESSURIZED METERED DOSE INHALERS AND PHARMACEUTICAL AEROSOL FORMULATIONS

(57) Abstract

Provided are pressurized metered dose inhalers containing stable formulations of a β–agonist drug in suspension or solution. Also provided are aerosol formulations suitable for inhalation therapy containing a β–agonist drug in suspension or solution.

Historically, ethanol concentrations greater than 5% have been used only for steroid-based formulations with hydrofluoroalkane propellants.

The ß-agonist drug, formoterol ("eformoterol" in Europe) and its derivatives, have proven difficult to formulate in conventional aerosols. Such formulations have exhibited short shelf-lives and require refrigeration. Refrigeration is undesirable because many patients are required to carry the aerosol canisters on their persons. There remains, therefore, an important need for aerosol formulations for ß-agonist drugs such as formoterol and its derivatives that remain chemically and physically stable during storage at ambient conditions of temperature and humidity.

SUMMARY OF THE INVENTION

An objective of the present invention is to provide a pressurized metered dose inhaler that contains a stable formulation of a ß-agonist drug, which does not require the use of refrigeration.

Another objective of the present invention is to provide a stable formulation of a ß-agonist drug that is suitable for use as an aerosol, which does not require the use of refrigeration.

The above objectives and other objectives are surprisingly achieved by the following. The present invention provides a novel pressurized metered dose inhaler comprising a container equipped with a metering valve and containing a pressurized aerosol formulation formulated from a composition comprising:

a ß-agonist drug;

at least one fluoroalkane propellant; and

greater than 5% by weight, based on total weight of the aerosol formulation, of a solvent that is capable of solubilizing or dissolving the ß-agonist drug.

The invention further provides a novel pressurized metered dose inhaler comprising a container equipped with a metering valve and containing a pressurized aerosol formulation formulated from a composition comprising:

particles of a ß-agonist drug;

at least one fluoroalkane propellant; and

a surfactant that is capable of forming a suspension of the particles of ß-agonist drug.

The invention also provides a novel aerosol formulation adapted for use in a pressurized aerosol container, said aerosol formulation being formulated from a composition comprising:

a ß-agonist drug;

at least one fluoroalkane propellant; and

greater than 5% by weight, based on total weight of the aerosol formulation, of a solvent that is capable of solubilizing or dissolving the ß-agonist drug.

The invention further provides a novel aerosol formulation adapted for use in a pressurized aerosol container, said aerosol formulation being formulated from a composition comprising:

particles of a ß-agonist drug;

at least one fluoroalkane propellant; and

a surfactant that is capable of forming a suspension of the particles of ß-agonist drug.

The aerosol formulations are surprisingly stable under conditions up to about 40°C and about 75% relative humidity for at least about four weeks.

BRIEF DESCRIPTION OF THE DRAWINGS

Fig. 1 illustrates a chromatogram of formoterol fumarate formulated as a suspension; and

Fig. 2 illustrates a chromatogram of the formoterol fumarate after storage for 28 days at 40°C and 75% relative humidity.

DETAILED DESCRIPTION OF THE INVENTION

It has been unexpectedly discovered that the stability of aerosol formulations of solutions of a ß-agonist drug can be significantly improved by utilizing more than 5% by weight of a solvent capable of solubilizing or dissolving the ß-agonist drug. The ß-agonist drug can be any form that is suitable for application to the lungs or nasal passages of a human, such as base form or weak acid form. The present invention will be described with reference to the ß-agonist drug formoterol. The term "formoterol" is hereinafter understood to mean the base form of formoterol as well as the weak acid form of formoterol, unless stated otherwise. A preferred weak acid form of formoterol is formoterol fumarate.

The amount of ß-agonist drug utilized in the aerosol formulation will depend on the type of drug selected. For formoterol fumarate, the concentration utilized is usually about 1% by weight or less, preferably about 0.01% to about 0.02% by weight, based on the total weight of the aerosol formulation.

Any solvent that is suitable for inhalation and capable of solubilizing or dissolving the selected ß-agonist drug can be used. Examples of suitable solvents include alcohols, ethers, hydrocarbons, and perfluorocarbons. Preferably the solvent is short chain polar alcohols. More preferably, the

solvent is an aliphatic alcohol having from one to six carbon atoms, such as ethanol and isopropanol. The most preferred solvent is ethanol. Examples of suitable hydrocarbons include n-butane, isobutane, pentane, neopentane and isopentanes. Examples of suitable ethers include dimethyl ether and diethyl ether. Examples of suitable perfluorocarbons include perfluoropropane, perfluorobutane, perfluorocyclobutane, and perfluoropentane.

The solvent is usually present in an amount of from about 6 % to about 30% by weight, based on the total weight of the aerosol formulation. Preferably, the solvent is present in an amount of about 10 % to about 15% by weight. Based on the disclosure provided herein, one skilled in the art will recognize that lower concentrations of medicament usually require lower concentrations of solvent, and vice versa, in order to form a stable solution.

Any fluoroalkane propellant that is suitable for inhalation can be used. Examples of suitable fluoroalkanes include HFA-134a, HFA-227ea, HFA-125 (pentafluoroethane), HFA-152a (1,1-difluoroethane), and HFA-32 (difluoromethane). Hydrocarbon and/or aliphatic gases may be added to modify propellant characteristics as required. Preferably, the aerosol formulation is substantially free of chlorofluorocarbons. However, if desired chlorofluorocarbons can be utilized.

The propellant for solution formulations is usually present in an amount of from about 70% to about 94% by weight, based on the total weight of the aerosol formulation. A preferred aerosol formulation comprises HFA-134a in an amount less than about 90% by weight, ethanol in an amount greater than about 10% by weight, and formoterol fumarate in an amount of about 0.01% by weight. A particularly preferred aerosol formulation comprises about 85 % by weight of HFA-134a, about 15 % by weight of ethanol, and about 0.01 % by weight of formoterol fumarate.

Pressurized metered dose inhalers are now well known in the art.

Any pressurized metered dose inhaler that is suitable for application of drugs to the lungs or nose of a patient can be used. Pressurized metered dose inhalers usually are equipped with a metering valve having a spray orifice diameter of about 460μm. However, with the higher concentrations of solvent employed in the present invention, it may be desirable that the solvent evaporates as soon as possible after inhalation. This can be achieved by reducing the spray orifice diameter, for example, to 250μm, in combination with using solvent concentrations of about 10 to about 15% by weight. Based on the disclosure provided herein, one skilled in the art will be able to adjust the component composition to deliver a desired dose for the selected metered valve, without undue experimentation. For example, the composition may be altered to adjust the vapor pressure of the formulation. The aerosol formulation and metering valve are usually selected to provide a therapeutically effective amount of the ß-agonist drug per activation. An example of a therapeutically effective amount of formoterol fumarate is about 12 μg per activation.

It has also been unexpectedly discovered that stable aerosol formulations of suspensions of particles of a ß-agonist drug can be formed by utilizing the ß-agonist drug in combination with a surfactant that is capable of forming a suspension of the ß-agonist drug particles. The present invention will be described with reference to the ß-agonist drug formoterol.

The propellant can be any of the propellants described herein with reference to solution aerosol formulations. However, the propellant in suspension aerosol formulations can be utilized in amounts up to about 99.9% by weight, based on the total weight of the aerosol formulation.

The amount of ß-agonist drug utilized in the aerosol formulation will depend on the type of drug selected. For formoterol fumarate, the concentration utilized is usually about 1% by weight or less, preferably about 0.01% to about 0.02% by weight, based on the total weight of the aerosol

formulation.

The particle size of the ß-agonist drug should be suitable for inhalation into the nose or lung. Suitable average particle sizes are about 100µm and less, preferably about 20µm and less, and more preferably in the range of about 1 to about 10µm.

Any surfactant that is suitable for application to the lungs of a patient and which is capable of forming a suspension of particles of the ß-agonist drug can be utilized. Examples of suitable surfactants include polyalcohols such as polyethylene glycol (PEG 300), diethylene glycol monoethyl ether (Transcutol), polyoxyethylene(20) sorbitan monolaurate (Tween 20) or monooleate (Tween 80), propoxylated polyethylene glycol (Antarox 31R1), polyoxyethylene 4-lauryl ether (Brij 30), and surfactants having similar HLBs. Preferably, the surfactant is polyoxyethylene 4-lauryl ether (Brij 30). The surfactant is usually present in an amount of about 1% by weight or less.

A preferred suspension formulation comprises HFA-134a in an amount greater than 99% by weight, Brij 30 surfactant in an amount of about 0.002% by weight or greater, and formoterol fumarate in an amount of about 1% or less. A particularly preferred suspension formulation comprises about 99 % by weight of HFA-134a, about 0.02 % by weight of Brij 30, and about 0.02% by weight of formoterol fumarate. A particularly preferred formulation in a 19 ml canister comprises about 12.6 g/canister of HFA-134a, about 0.002 g/canister Brij 30, and about 0.002 g/canister of formoterol fumarate.

The following examples are presented merely to illustrate particular embodiments of the invention and not to limit the claims which are supported by the entire specification.

Examples I-3

Three suspension aerosols according the present invention were

Table 6

Test		Example 18	Example 19
Unit Spray Content	Drug per Dose (mcg)	10.87	9.55
	Material Balance (%)	89.0	78.5
	Shot Weight (mg)	78.6	78.0
	Shot Number	6-7	71-72
Unit Spray Content	Drug per Dose (mcg)	10.51	12.90
	Material Balance (%)	86.0	104.8
	Shot Weight (mg)	78.7	78.9
	Shot Number	8-9	73-74
Andersen Impactor	Valve (mcg)	5.93	9.14
	Actuator/Adapter (mcg)	28.91	29.02
	Induction Port/Cone (mcg)	30.03	20.18
	Stage 0 (mcg)	1.33	0.96
	Stage 1 (mcg)	1.64	1.32
	Stage 2 (mcg)	2.28	1.72
	Stage 3 (mcg)	9.54	8.45
	Stage 4 (mcg)	29.37	27.25
	Stage 5 (mcg)	27.71	27.52
	Stage 6 (mcg)	3.27	3.38
	Stage 7 (mcg)	0.00	0.00
	Stage F (mcg)	0.68	0.00
	Total S0-S7 (mcg)	75.14	70.60
	Total Drug Recovered (mcg)	140.69	128.93
	Material Balance (%)	107.7	103.8
	MMAD	2.3	2.5
	GSD	1.6	1.5
	Fine Particle Dose (mcg)	73	68
	Fine Particle Fraction (%)	69	75

Andersen Impactor	Valve (mcg)	5.64	-
	Actuator/Adapter (mcg)	28.58	-
	Induction Port/Cone (mcg)	23.56	-
	Stage 0 (mcg)	1.13	-
	Stage 1 (mcg)	1.56	-
	Stage 2 (mcg)	1.97	-
	Stage 3 (mcg)	9.95	-
	Stage 4 (mcg)	30.04	-
	Stage 5 (mcg)	27.51	-
	Stage 6 (mcg)	3.05	-
	Stage 7 (mcg)	0.00	-
	Stage F (mcg)	0.00	-
	Total S0-S7 (mcg)	75.21	-
	Total Drug Recovered (mcg)	132.98	-
	Material Balance (%)	103.3	-
	MMAD	2.5	-
	GSD	1.5	-
	Fine Particle Dose (mcg)	73	-
	Fine Particle Fraction (%)	74	-
Formulation	HFA-134a	12.8169	12.6705
	Brij 30	0.00230	0.00220
	Formoterol fumarate	0.002044	0.001970

While the invention has been described in detail and with reference to specific embodiments thereof, it will be apparent to those of ordinary skill in the art that various changes and modifications can be made to the claimed invention without departing from the spirit and scope thereof.

5

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
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Folios	26

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

No. Sol. Internacional PCT /EP03/01964
Fecha de Presentación Internal. Febrero 26 de 2003

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

1.1. Descripción: Folios: 32 a 68 como se radicó inicialmente.

1.2. Reivindicaciones: 1 – 22. Folios: 69 a 73 como se radicó inicialmente.

1.3 Dibujos: Folios: 91 a 92 como se radicó inicialmente.

1.5. Prioridad: EP 02004786.6 de 01/03/2002 y EP 02023589.1 de 23/10/2002.

2. Objeto de la invención

Título de la solicitud: " **Formulación superfina de Formoterol** "

El **objeto de la presente solicitud** de patente de invención, es proporcionar una formulación farmacéutica que comprende como agente activo formoterol en una solución de propelente HFA licuado y un cosolvente.

- *Reivindicaciones 1 – 21:* Formulación de aerosol farmacéutico para administración mediante inhaladores que comprende como agente activo como formoterol en una solución de propelente HFA licuado y un cosolvente.

- *Reivindicación 22:* Método para preparar las formulaciones de las reivindicaciones anteriores.

El **problema planteado** en esta solicitud es la necesidad de proveer formulaciones de formoterol estables y altamente eficientes para ser administradas mediante pMDI con una penetración mas profunda en el pulmón y con un tamaño de partícula tal que garantice la uniformidad de la dosis.

Para **solucionar este problema técnico,** la solicitud en estudio proporciona una formulación de solución de aerosol farmacéutico para administración mediante pMDI que contiene formoterol como ingrediente activo, un propelente HFA y un cosolvente para la solubilización del fármaco, con una cantidad de agua residual menor a 1500 ppm y una fracción de partículas con diámetro igual o menor a 1.1 micras.

- El objeto de la invención definido anteriormente se clasificó de acuerdo con el IPC así: A61K9/00, A61K31/485.

3. De la solicitud de Patente

3.1. Reivindicaciones *(artículo 30 D 486)*

Esta Oficina se permite señalar que dentro de las reivindicaciones se encontró falta de claridad debido a que:

- *Reivindicación 4:* La forma farmacéutica de la presente reivindicación se está definiendo mediante el contenido de la prueba de un método referenciado en la descripción, la cual no es una característica técnica esencial. Por lo tanto, se recuerda al solicitante que una forma farmacéutica debe estar definida por sus componentes y cantidades, y debe ser clara por si misma, en este sentido, no debe hacer alusión a datos citados en el capitulo descriptivo de la solicitud.

- *Reivindicaciones 16, 20 - 21*: La formulación farmacéutica de las presentes reivindicaciones se está caracterizando por el recipiente donde es introducida y no por sus características técnicas esenciales como componentes y cantidades. Por lo tanto, se solicita aclarar al interesado el alcance de protección de estas reivindicaciones, ya que se observan claramente dos conceptos inventivos totalmente diferentes: la formulación farmacéutica y el recipiente en el cual es introducida.

A través de todo el capitulo reivindicatorio, se observa la posibilidad de obtención de varias formulaciones farmacéuticas, sin embargo, en el capitulo descriptivo, solo existen dos ejemplos de prueba. Por lo tanto, se solicita al interesado definir con claridad y concisión cual o cuales son las formulaciones farmacéuticas que desea proteger, las cuales debieran estar sustentadas con los respectivos resultados de las pruebas de eficacia.

4. Determinación del Estado de la Técnica

La fecha que se ha tenido en cuenta para determinar el Estado de la Técnica es la fecha de presentación de la solicitud prioritaria: 01/03/2002

Teniendo en cuenta la fecha indicada se realizó la búsqueda en el estado de la técnica de documentos relacionados con la solicitud encontrándose los siguientes documentos más relevantes:

Nº	Documento	Título	Fecha de publicación*
D1	EP1157689	**Stable pharmaceutical solution formulations for pressurised metered dose inhalers**	28/11/2001
D2	WO9965460	**Pressurized metred dose inhalers and pharmaceutical aerosol formulations**	23/12/1999

Documento **D1** folios 125 a 134 y **D2** folios 135 a 143.

5. Análisis de patentabilidad (artículo 14 D486)

5.1. Nivel inventivo *(artículo18 D486)*

- **Las reivindicaciones 1 a 21** se refieren a una formulación de aerosol farmacéutico para ser administrada mediante inhaladores de dosis medidas presurizadas que comprende: **a)** un ingrediente activo seleccionado de formoterol, formoterol fumarato o un estereoisómero, sal y solvato fisiológicamente aceptables de los mismos, en una solución de **b)** un propelente HFA licuado como HFA 134a y HFA 227, y **c)** un cosolvente del tipo de polioles, polialquilenglicoles o

alcoholes como etanol anhidro; caracterizada porque la cantidad de agua residual es menor a 1500 ppm en el peso total de la formulación, además porque la concentración de etanol está comprendida entre 10 y 20% P/P, la de fumarato de formoterol en un rango de 0.003 y 0.192% P/V y la de HCl es de 0.037% P/P; y porque puede comprender además otro ingrediente activo como un esteroide o un derivado anticolinérgico tipo atropina.

El nivel inventivo de dicha **formulación** se ve afectado por el siguiente documento más cercano encontrado en el Estado de la Técnica:

D1 que es el estado de la técnica más cercano, enseña composiciones farmacéuticas estables en solución para ser usadas con inhaladores de dosis medidas presurizadas, adecuadas para administración en aerosol. Dichas composiciones contienen: **a)** un principio activo agonista β_2 como formoterol o uno de sus correspondientes estereoisómeros (Folio 128), **b)** un propelente HFA licuado como HFA 134a y HFA 227 (Folio 126) **c)** un cosolvente seleccionado de alcoholes como etanol para solubilizar el fármaco (Folio 126). Estas formulaciones en solución, ofrecen la ventaja de permanecer homogéneas ya que el ingrediente activo y los excipientes están completamente disueltos en el vehículo propelente o su mezcla con un cosolvente adecuado como el etanol, asegurando asi una mayor consistencia en la uniformidad de la dosis (Folio 126). Adicionalmente, las formulaciones de la anterioridad pueden contener:

- un **acido mineral** como **HCl** 1.0 M para ajustar el pH, el cual oscila entre 2.5 y 5.0 (Folio 126, 129), el cual se encuentra en una cantidad entre 3.0 y 3.5 µL (Folio 129 y ejemplos 3 – 6).
- opcionalmente, un componente de baja volatilidad como **propilenglicol, polietilenglicol** con una cantidad de agua residual menor al 0.1% V/V, para modular el MMAD de las partículas de aerosol y mejorar la estabilidad de la formulación (Folio 127, 129).
- **Etanol** como cosolvente en una cantidad de 12% V/V (Folio 127).
- **Formoterol fumarato** 6 – 12 µM/dosis, equivalentes a 1.92 mg y 0.019% P/V de la formulación del folio 62 de la presente solicitud (Folio 129 y ejemplos 2 – 6).

D1 también enseña que las formulaciones de la invención están contenidas en un **cartucho** que tiene parte de o todas sus superficies internas completamente de alumnio anódico, acero inoxidable o con un recubrimiento orgánico inerte (Folio 129).
Adicionalmente en el folio 128, divulga como **combinaciones** para aerosol de corta o larga duración, de formoterol y TA 2005, entre otros agonistas β_2, con: a) esteroides como beclometasona dipropionato, fluticasona propionato y budesonida y b) anticolinérgicos derivados de atropina como bromuro de ipratropio, bromuro de tiotropio y bromuro de oxitropio; son ampliamente en el estado de la técnica.

La formulación reivindicada en la clausula 1, se diferencia de **D1** por la mención de cantidad de agua residual, la cual es menor a 1500 ppm en el peso total de

la formulación.

Sin embargo, el efecto técnico conseguido por esta diferencia es el mismo, ya que ambas formulaciones proveen formulaciones de formoterol estables y con uniformidad de dosis.

El problema técnico objetivo de la solicitud es cómo proporcionar formulaciones de formoterol estables y altamente eficientes para ser administradas mediante pMDI con una penetración mas profunda en el pulmón y con un tamaño de partícula tal que garantice la uniformidad de la dosis.

D2 enseña formulaciones estables en solución contenidas en inhaladores de dosis medidas presurizadas, que comprenden: **a)** un fármaco β-agonista como formoterol, formoterol fumarato en una cantidad entre 0.01% a 0.02% por peso, sobre el peso total de la formulación y con un tamaño de partícula adecuado para inhalación en un rango de 1 a 10 µM (136, 138, 141), **b)** un propelente tipo fluoroalcano como HFA-134a o HFA-227 (Folio 136, 139); y **c)** un solvente capaz de solubilizar el fármaco β-agonista, como etanol, en una cantidad que oscila en el rango de 6% a 30% (Folio 136, 139). Además muestra como ejemplo de cantidad terapéuticamente eficaz de formoterol fumarato 12 µM por activación (Folio 140). **D2** enseña en los ejemplos de la tabla 6, formulaciones con un % de fracción fina de partículas de principio activo 1 a 10 µM que oscila entre 69%, 75% 74%, superior al 50% reivindicado en la clausula 5 de la presente solicitud (Folios 135 a 143).

Teniendo en cuenta que en **D1** se describe una forma para solucionar el problema técnico, a saber, una formulación de formoterol estable y altamente eficiente para ser administrada mediante pMDI con una penetración mas profunda en el pulmón y con uniformidad de dosis; el experto en la materia motivado por proveer una solución al problema planteado, podría obtener la formulación de la reivindicación 1 y sus dependientes 2 a 21, a partir de las formulaciones presentes en **D1** y con la información que de allí se obtiene como la inestabilidad inherente del formoterol frente a condiciones oxidativas y de solvólisis debido a la presencia de vehículos polares, y por ende la utilización de solventes apróticos como el vehículo HFA-etanol, en donde los protones son no-hidratados, para lograr obtener una formulación con baja cantidad de agua residual o humedad que como es bien sabido afecta la estabilidad del formoterol en el almacenamiento (Folio 3); y con el tamaño de partícula y % de fracción fina que se muestra en las formulaciones de **D2,** en el cual está comprendido el tamaño de partícula de las formulaciones en estudio. Además del conocimiento que la solubilidad de un principio activo se puede incrementar con la adición de un cosolvente, lo cual es importante, ya que la baja solubilidad de un principio activo puede impedir su administración en altas dosis y por ende la necesidad de medidas como la reducción del tamaño de partícula del activo.

Por lo tanto, la formulación reivindicada en la clausula 1 y sus dependientes 2 a 21, se constituye en una alternativa para proveer formulaciones en solución para administración mediante pMDI.

Asi las cosas, la formulación farmacéutica de las reivindicaciones 1 a 21, no es inventiva.

- **La Reivindicación 22** se refiere a un método para preparar las formulaciones de las reivindicaciones anteriores que comprende: **a)** preparación de una solución de uno o mas ingredientes activos en uno o más cosolventes; **b)** de manera opcional, ajustar el pH de la solución; **c)** llenar el dispositivo con la solución; **d)** fruncir con válvulas y gaseamiento y **e)** agregar un propelente que contiene un hidrofluoroalcano (HFA).

El nivel inventivo de dicho **método** se ve afectado por el siguiente documento más cercano encontrado en el Estado de la Técnica:

D1 que es el estado de la técnica más cercano, enseña un método de llenado de un inhalador para aerosol con una composición, que comprende: **a)** preparación de una solución de uno o mas ingredientes activos en uno o mas cosolventes opcionalmente conteniendo una cantidad apropiada de componente de baja volatilidad; **b)** llenado del dispositivo con dicha solución; **c)** adición de una cantidad predeterminada de un acido mineral fuerte; **d)** adición de un propelente que contiene un hidrofluoroalcano (HFA) y **e)** fruncir con válvulas y gastamiento (Folio 4).

El método reivindicado en la clausula 22, se diferencia de **D1** porque primero se frunce con válvulas y gastamiento (etapa **e**) y luego se agrega el propelente que contiene un hidrofluoroalcano (HFA) (etapa **d**).

Sin embargo, el efecto técnico conseguido por esta diferencia es el mismo, ya que ambas formulaciones se suministran de la misma manera, a saber en forma de aerosol, mediante el sistema pMDI.

El problema técnico objetivo de la solicitud es cómo proporcionar formulaciones de formoterol estables y altamente eficientes para ser administradas mediante pMDI con una penetración mas profunda en el pulmón y con un tamaño de partícula tal que garantice la uniformidad de la dosis.

Teniendo en cuenta que en **D1** se describe una forma para solucionar el problema técnico, a saber, proporcionar una formulación para ser administrada mediante pMDI; el experto en la materia podría obtener el método de la reivindicación 22, a partir del descrito en **D1,** al intercambiar el orden de las etapas d) y e), en esta medida primero se frunce con válvulas y gastamiento (etapa **e**) y luego se agrega el propelente que contiene un hidrofluoroalcano (HFA) (etapa **d**).

Por otra parte, no se observa la ventaja comparativa pretendida por el solicitante al proveer el método reivindicado ya que no se presenta un estudio que sustente la ventaja de llevar a cabo las etapas en el orden reivindicado y no como en la anterioridad **D1**.

Asi las cosas, el método de la reivindicación 21 no es inventivo.

13. Conclusión:

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

N°	Documento N°	Reivindicaciones afectadas	Requisito que afecta
D1	EP1157689	1 - 21	Nivel inventivo
D2	WO9965460	1 - 21	Nivel inventivo

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
Jefe de División de Nuevas Creaciones

El anterior requerimiento fue notificado por fijación en lista, de fecha 27 JUN. 2008

CONCEPTO TÉCNICO No. 1493	**EXAMINADOR TÉCNICO** Código No. 202071